Antimicrobial Stewardship Practices in the Emergency Department of a South African Tertiary Institution: Patterns and Appropriateness of Antimicrobial Prescribing

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Pharmacy.

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Johannesburg, 2024.

Declaration

I, Bronwen Anette Wodrich, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Bronwen Anette Wodrich

30th day of June 2025 in Johannesburg

Ethics declaration

I, Bronwen Anette Wodrich, declare that I am registered with the University of the Witwatersrand for the degree in Master of Pharmacy and have read the University's current research ethics guidelines. I accept responsibility for the conduct of the procedures in accordance with the University of the Witwatersrand Human Research Ethics Committee (WITS-HREC). I have obtained ethical approval from WITS-HREC (M210335, Appendix A) and received permission from the Helen Joseph Hospital Ethics and Research Committee to conduct this research (Appendix B).

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Bronwen Anette Wodrich

30th day of June 2025 in Johannesburg

Dedication

A dedication to my parents, Jennifer and Rainer Wodrich, who supported me through this process along with their love and patience.

Abstract

Antimicrobial resistance is a global health issue, exacerbated by the misuse and overuse of antimicrobials. Emergency departments are crucial settings for antimicrobial stewardship (AMS) efforts due to their high rate of antimicrobial prescribing and risk of misuse. There is a need to research antimicrobial prescribing in South African emergency departments due to insufficient data on appropriate prescribing rates in these settings. This study aimed to determine the patterns and appropriateness of antimicrobial prescribing by physicians in the emergency department of a tertiary public institution.

A retrospective review was conducted for the period of August 2020 to July 2021 of patient medical records from the emergency department of a tertiary public academic hospital in South Africa. Patient medical records were reviewed and included if antimicrobials were prescribed or indicated based on the diagnosis. The Medicine Appropriateness Index (MAI) tool was used to evaluate these prescriptions' appropriateness against the South African Standard Treatment Guidelines (STG), the South African Antibiotic Stewardship Programme (SAASP), and the South African Medicines Formulary (SAMF).

Eight hundred and fifty (n=850) patient medical records were reviewed. Among the reviewed patient medical records with guideline-listed diagnoses only 9.6% (n=76/790) of antimicrobial therapies were fully appropriate according to the STG, 8.0% (n=33/415) according to the SAASP and 10.6% (n=43/407) according to the SAMF, as per the MAI tool. The most frequent reasons for inappropriate antimicrobial prescriptions included the choice of antimicrobial (STG: 61.3%; SAASP: 53.0%; SAMF: 53.0%), cost (STG: 51.0%; SAASP: 66.9%; SAMF: 65.3%), inappropriate duplication of spectrum of activity (STG: 63.1%; SAASP: 66.9%; SAMF: 65.3%), and the duration of treatment (STG: 32.5%; SAASP: 54.9%; SAMF: 43.1%). The conditions groups leading to the most emergency department visits and inappropriate antimicrobial prescriptions included skin and soft tissue (19.8%), trauma and injuries (19.2%), lower respiratory tract (15.7%), urinary tract (12.2%) and reproductive system conditions (11.2%). The most frequent antimicrobials prescribed were amoxicillin/clavulanic acid (54.7%), azithromycin (11.1%), metronidazole (6.8%), ceftriaxone (6.2%) and ciprofloxacin

(4.6%). The main reasons for the inappropriate prescribing of these common antimicrobials were the incorrect choice, duration, strength and frequency.

The vast majority of antimicrobial prescriptions were inappropriate according to guidelines (STG: 90.4%; SAASP: 92%; SAMF: 89.4%) which highlights the urgent need to establish a functional AMS programme in this emergency department. Key elements contributing to inappropriate antimicrobial prescriptions (such as the choice, cost, spectrum duplication and treatment duration) could benefit from focused AMS interventions. Another area of focus would be to optimise the rational use of amoxicillin/clavulanic acid, given its high prevalence (89.0% of prescribed penicillins) and the frequent issues with inappropriate treatment selection and duration. Overall, these findings emphasise the pressing need for a comprehensive AMS programme to ensure a larger percentage of antimicrobials are prescribed appropriately and within guidelines.

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List of abbreviations

AIDS: Acquired immunodeficiency syndrome

AMR: Antimicrobial resistance

AMS: Antimicrobial stewardship

ASP: Antimicrobial stewardship programme

BRICS: Brazil, Russia, India, China and South Africa

CAP: Community-acquired pneumonia

CDC: Centres for Disease Control and Prevention

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

DDD: Defined daily dose

ED: Emergency department

EDL: Essential drug list

ENT: Ear, nose and throat

GAP: Global Action Plan

GERMS-SA: Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa

GLASS: Global Antimicrobial Resistance Surveillance System

GUS: Genital ulcer syndrome

HIV: Human Immunodeficiency Virus

ICD: International Classification of Diseases

IDSA: Infectious Diseases Society of America

IPC: Infection Prevention and Control

LMICs: Low-middle-income countries

LRTI: Lower respiratory tract infection

MAI: Medicine Appropriateness Index

MDR: Multi-drug resistant

MRSA: Methicillin-resistant *Staphylococcus aureus*

MUS: Male urethritis syndrome

NDoH: National Department of Health

NICD: National Institute for Communicable Diseases

PCT: Procalcitonin

PID: Pelvic inflammatory disease

PIDS: Paediatric Infectious Diseases Society

REDCap: Research Electronic Data Capture

SAASP: South African Antibiotic Stewardship Programme

SAMF: South African Medicines Formulary

SAPC: South African Pharmacy Council

SD: Standard deviation

SHEA: Society for Healthcare Epidemiology of America

SSTI: Skin and soft tissue infection

STG: Standard Treatment Guidelines

STI: Sexually transmitted infection

TB: Tuberculosis

URTI: Upper respiratory tract infection

USA: United States of America

UTI: Urinary tract infection

VDS: Vaginal discharge syndrome

WCC: White blood cell count

WHO: World Health Organisation

WITS-HREC: University of the Witwatersrand Human Research Ethics Committee

Chapter 1: Introduction

This introductory chapter discusses the impact of antimicrobial resistance (AMR) globally and the rationale for antimicrobial stewardship (AMS), specific to the public healthcare sector in South Africa. This chapter states the pharmacists' roles in the multi-disciplinary team working in an antimicrobial stewardship programme (ASP) and the need for these programmes in outpatient settings, such as the emergency department (ED). This chapter looks briefly into the current South African context of AMR, ASPs and the pharmacists' potential influences therein.

1.1 Research context

1.1.1 Antimicrobial resistance

Antimicrobial resistance is a current public health challenge globally (Centers for Disease Control and Prevention, 2019a; World Health Organization, 2022b). Approximately 700 000 people die each year due to AMR and, if no action is taken, this number is expected to rise to ten million by 2050 (O'Neill, 2014; Murray et al., 2022). Microorganisms (including bacteria, viruses, fungi and parasites) are able to evolve in order to survive different circumstances. This is the outcome of natural selection and genetic strategies such as spontaneous mutations and plasmid exchange (Center for Disease Dynamics, Economics & Policy, 2015; Penesyan et al., 2015). Although, AMR occurs naturally in microorganisms regardless of exposure to antimicrobials, increased antimicrobial pressure or antimicrobial-induced natural selection accelerates the evolution and growth of resistant mutants (Reygaert, 2018; Michael et al., 2021).

Antimicrobial misuse and overuse are, therefore, considered significant contributors to AMR (Fishman et al., 2012; Laxminarayan et al., 2013; Mir et al., 2019). Antimicrobial misuse is also responsible for suboptimal treatment, higher healthcare costs and preventable drug toxicity (Davey et al., 2017; Parente et al., 2017). The misuse and overuse of antimicrobials can lead to co-selection resistance, where the use of one antimicrobial can result in the selection of pathogen strains that are co-resistant to other antimicrobials (Karakonstantis and Kalemaki, 2019). This leads to pathogens exhibiting resistance to entire classes of antimicrobials, or across different classes with overlapping drug targets or drug efflux pumps. One class of antimicrobials can also promote resistance to other classes through enhanced mutagenesis (Kohanski et al., 2010; Cherny et al., 2020). A microorganism is labelled multi-drug resistant

(MDR) when it shows resistance to at least one agent in three or more antimicrobial categories (Magiorakos et al., 2012; Magira et al., 2018). Infections caused by MDR microorganisms result in longer hospital stays, increased mortality and morbidity and negatively impacts countries' economies due to increased health care costs, increased absence from work, and a reduced healthy workforce (Donnelly et al., 2014; World Health Organization, 2014; Center for Disease Dynamics, Economics & Policy, 2015). The limited number of new antimicrobials in development highlights the importance of using existing antimicrobials appropriately to preserve their efficacy (World Health Organization, 2019a; Iskandar et al., 2022; Salam et al., 2023).

1.1.2 Antimicrobial stewardship

Antimicrobial stewardship was first mentioned in a published article in 1996 by McGowan Jr and Gerding, in the United States of America (USA). The authors emphasised the need to preserve antimicrobials and to consider them as non-renewable resources (McGowan Jr and Gerding, 1996). This is still true today, as the World Health Organisation (WHO) annually reports the analysis of the few antibacterial agents in pre-clinical and clinical development (World Health Organization, 2022a). The report, published for the year 2021, states that only 12 new antibiotics were approved from the start of July 2017, but nearly all newly approved agents have limited clinical benefit over existing treatment; and that over 80% of these agents already belong to existing antibiotic classes, where resistance mechanisms are present (World Health Organization, 2022a). The WHO (2022) believes the clinical pipeline and newly approved antimicrobial agents fail to meet the current, rapidly developing AMR and respective challenges. In addition to these reports, the WHO aims to guide countries to develop and implement ASPs to reserve the use of all types of antimicrobials (World Health Organization, 2021c, 2021a). The term "antimicrobial stewardship" has gained significant traction in recent years, even though similar programs existed in individual hospitals during the 1990s and 2000s (Dyar et al., 2017a). Leaders of these programmes were either pharmacists, specialists of infectious diseases or clinical microbiology along with pharmacists, and entailed intervention strategies such as prior authorisation before initiation of antibiotics, restricted antibiotic formularies, education of healthcare professionals and infection-control measures (Dyar et al., 2017a; Kazanjian, 2017).

Antimicrobial stewardship is defined as systematic interventions constructed to improve and measure the appropriate use of antimicrobial agents by ensuring the correct choice of antimicrobial agent, dose, duration and route of administration (Fishman et al., 2012; Barlam et al., 2016). Interventions are intended to alleviate AMR, prevent adverse effects of these agents, reduce length of hospital stays, reduce healthcare costs and improve patient outcomes (May et al., 2013; Barlam et al., 2016; Davey et al., 2017). Evidence shows that ASPs reduced healthcare costs, community resistance rates and have improved patient outcomes (Dinh et al., 2017; Kaufman et al., 2017). Antimicrobial stewardship uses evidence-based guidelines to support the rational use of antimicrobials (Gasson et al., 2018).

Antimicrobial stewardship programmes are established and led by a team of multi-disciplinary healthcare professionals, inclusive of clinical pharmacists, and most commonly within inpatient settings (Newland et al., 2014; Barlam et al., 2016). Pharmacists work within this healthcare team to improve antimicrobial management, identify potential prescribing errors and educate other healthcare professionals about the safer and more effective use of these medicines (Baker et al., 2012; May et al., 2013; Ourghanlian et al., 2020). Furthermore, pharmacists must ensure that prescribers are adopting the locally relevant and rational antimicrobial prescribing guidelines to ensure optimal antimicrobial therapy and an absence of prescription errors (Essack et al., 2011; Garau and Bassetti, 2018). Pharmacists should be available to provide interventions based on high quality, evidence-based information (Essack et al., 2011; Lowrie et al., 2014; Riordan et al., 2017).

1.1.3 Outpatient AMS

Antimicrobial stewardship programmes have repeatedly demonstrated positive influences with inpatient settings; however, literature observing the impacts these interventions in outpatient and emergency care settings are still needed (Gerber et al., 2013; May et al., 2013; Mistry et al., 2015). Antibiotic prescribing in outpatient settings surpasses that of inpatient prescribing (Fleming-Dutra et al., 2016; Sanchez et al., 2016). It is estimated that 54–90% of all antimicrobials prescribed within a healthcare system are for outpatient settings, with antibiotics being prescribed in nearly 13% of emergency care visits (Suda et al., 2013; Sanchez et al., 2016; Palms et al., 2018). Studies, however, indicate that approximately 23–76% of these prescriptions are inappropriate (Havers et al., 2018; Shively et al., 2018).

Outpatient AMS is rapidly rising in current practices, with research geared toward interventions to prevent AMS. There are a number of challenges, however, to establish outpatient ASPs. Its isolated setting makes it difficult because there is a lack of leadership commitment, dedicated persons or qualified personnel to supervise these programmes and provide guidance on effective interventions and implementations (Bork et al., 2020; Eudy et al., 2020; Dumkow, 2024). Another challenge is the lack of standardised prescribing practices, especially amongst different specialities (Dumkow, 2024). Examples of areas of focus for these settings include unnecessary and suboptimal antimicrobial prescribing, and identifying factors associated with inappropriate antimicrobial prescribing (Bork et al., 2020). It is imperative to report and track prescribing practices in order to compare and measure against current published treatment guidelines and evidence-based medicine literature (Sanchez et al., 2016; Bork et al., 2020). Once this information is gathered it can be used, together with published regulations and guidelines, to develop AMS interventions (Bork et al., 2020). Suggested AMS interventions from research include patient education, prescriber education, active monitoring, delayed prescribing, antimicrobial audits and feedback, and a focus on syndrome-specific, special patient populations and specific antibiotic interventions (King et al., 2018; Bork et al., 2020). Literature is steadily emerging for AMS and the impact of ASP in several outpatient settings, however, insight into the need and feasibility of these principles is still required for EDs.

Due to the increasingly high number of prescriptions for antimicrobials in recent years, the ED has been targeted for researching AMS interventions in various countries (Bishop, 2016; Pulia et al., 2018; Yadav et al., 2019). A high prevalence of inappropriate antibiotic prescribing in the ED is evident in cases of upper respiratory tract, urinary tract and skin and soft tissue infections (SSTIs) (Pulia et al., 2018). In the USA, it is reported that 30% to 50% of inappropriate antibiotic prescriptions occur because of incorrect choices of class of antibiotic, durations of use and respective doses (Fleming-Dutra et al., 2016; Sanchez et al., 2016; Timbrook et al., 2017). A retrospective monocentric study reported that approximately 60% of antibiotic prescriptions were inappropriate due to prescribers having overlooked guidelines (Grenet et al., 2016). If a patient receives inappropriate antimicrobials, they face the risk for clinical failure, additional visits to healthcare facilities or admission to the hospital (Dumkow et al., 2017). In 2013 to 2014, in the USA, 16% of patients with adverse drug events presenting to the ED were caused by antimicrobials (Shehab et al., 2016). The rapid-pace and stressful environment of the ED, characterised by high patient and staff turnover makes this setting challenging to implement ASPs (Bishop, 2016; Acquisto and May, 2020). The need for quick decision making and limited diagnostic information available makes it difficult for prescribers, especially less experienced interns or new staff, to read resources and guidelines present if not quickly accessible (Acquisto and May, 2020; Ruiz-Ramos et al., 2023).

1.1.4 South African context of AMR and AMS

Antimicrobial resistance has serious consequences for resource-limited, low- and middle-income countries (LMICs), such as South Africa, where poverty increases risk for infections (Laxminarayan et al., 2013; Alsan et al., 2018). In the African region, there are reports of increasing AMR and MDR microorganisms being transmissible in the hospital and community environments (World Health Organization, 2014). South Africa is vulnerable to the effects of AMR due to the higher burden of communicable diseases including drug-resistant bacteria, fungi, human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), and tuberculosis (TB), alongside a rise in non-communicable diseases (Meyer et al., 2017; Academy of Science of South Africa, 2019; Chetty et al., 2019). Unfortunately, South Africa is also recognised as a nation with a high consumption of antibiotics, particularly those with a broad spectrum (Van Boeckel et al., 2014; Chetty, 2021). South Africa's healthcare system is comprised of both private and public healthcare sectors, where the public healthcare sector is predominantly funded by government and supplies healthcare access to 84% of South Africans (Meyer et al., 2017; Schellack et al., 2017). The National Department of Health (NDoH), responsible for implementing the national health policy, has acknowledged the danger of AMR and, as a result, have released the AMR Strategy Framework (National Department of Health, 2014, 2017). This framework functions to appoint accountability, roles and responsibilities to persons for the aim of undertaking the AMR issue and strategies such as surveillance, infection prevention and control and AMS (National Department of Health, 2017).

In a scoping review of the literature of AMS initiatives or strategies employed in South African healthcare sectors, it has been highlighted that AMS interventions in the public sector are facility specific and physician led (Boyles et al., 2013, 2017). The barriers faced for implementation of many of these AMS interventions include lack of expertise for leadership, geographical discrepancies, limited resources and understanding factors for local prescribing patterns (Brink et al., 2016; Scheepers et al., 2023). There is limited surveillance data on the use of antimicrobials at provincial, local, district and institutional levels due to lack of integration of pharmaceutical services, laboratory and clinical information (Engler et al., 2020; Mthombeni et al., 2022). Studies in South Africa where pharmacist-driven interventions, however, showed a decreased use of average antimicrobial use, improved patient care, and improved compliance and pharmacists were influential in resolving medicine-related problems in inpatient settings (Brink et al., 2016; Bronkhorst et al., 2014). Further research is required to assess the pharmacist's AMS role in South African outpatient settings.

1.2 Purpose of study

Almost no studies have determined the need or presence of AMS interventions in EDs in South African tertiary public hospitals. By determining appropriateness of antimicrobial prescribing patterns within the ED setting, new opportunities for AMS interventions can be highlighted, such as prescriber education and clinical-decision support by easily accessible guidelines in the ED (King et al., 2018; Bork et al., 2020). This would benefit public health due to South Africa's overwhelmed healthcare sector, which suffers from high morbidity and mortality rates, as it would enhance patient outcomes and lead to cost savings (Losier et al., 2017; Al-Omari et al., 2020; Sapozhnikov et al., 2024). Pharmacists would be ideal to assist in these interventions, because they are well equipped to manage ASPs and are readily available within health institutions (Bronkhorst et al., 2014; Schellack et al., 2016).

1.3 Aim

This study aimed to determine the patterns and appropriateness of antimicrobial prescribing by physicians in the ED of the tertiary public institution, Helen Joseph Hospital.

1.4 Research objectives

1.4.1 To determine the antimicrobial prescribing patterns of prescribing physicians in the ED of Helen Joseph Hospital by using the Medicine Appropriateness Index (MAI) tool.

1.4.2 To determine the appropriateness of antimicrobials prescribed per prescription in accordance with South African Standard Treatment Guidelines (STG), South African Antibiotic Stewardship Programme (SAASP) and South African Medicines Formulary (SAMF).

Chapter 2: Literature review

2.1 Impact of AMR

Antimicrobial resistance presents a global crisis with far-reaching impacts on public health, economy and healthcare systems (Sartelli et al., 2020). It leads to increased mortality and morbidity as infections become harder to treat and significantly elevate healthcare costs globally. By 2050, it is estimated that AMR may cause 300 billion to one trillion-dollar loss of capital globally. According to the Centres for Disease Control and Prevention (CDC) over 2.8 million people in the USA fall ill to diseases with antibiotic-resistant microorganisms annually leading to a minimum of 35 000 deaths (Morrison and Zembower, 2020). According to the CDC, AMR contributes to an additional 20 billion dollars in direct healthcare costs and leads to an annual loss of approximately 35 billion dollars in productivity (Prestinaci et al., 2015; Llor and Bjerrum, 2016; Dadgostar, 2019). In the WHO member state region of the Americas (including North and South America), substantial AMR burden was due to *Escherichia coli and Staphylococcus aureus* with each contributing to over a 100 000 deaths associated with AMR (Aguilar et al., 2023). In Europe, it is estimated that AMR has cost the healthcare system more than nine billion euros per year with more patients having pan-resistant organisms in intensive care, haematology and transplant units. The WHO European region is estimated to make up 10.5% and 10.9% of global deaths attributable to and global deaths associated with AMR, respectively (Mestrovic et al., 2022). *Escherichia coli* and *Staphylococcus aureus* present the largest burden of AMR in this region (European Centre for Disease Prevention and Control and World Health Organization, 2022; Mestrovic et al., 2022). In 15 European countries, over 10% of bloodstream *Staphylococcus aureus* infections are due to methicillin-resistant strains, with some of these countries experiencing rates as high as 50%. *Klebsiella pneumoniae* has also demonstrated a significant burden leading to 20 000 deaths due to AMR and almost 70 000 deaths associated with AMR in 2019 (Mestrovic et al., 2022). The rapid global dissemination of resistant strains underscores the need for international cooperation in addressing this threat. The development of new antimicrobials is lagging, further complicating efforts to combat resistant organisms. Antimicrobial resistance intensifies social inequalities and strains healthcare policies, demanding a comprehensive and coordinated response that spans public health initiatives, policy reforms and increased research and surveillance (Jamrozik and Selgelid, 2020; Patel et al., 2023).

A systematic analysis of bacterial AMR globally estimated the highest rates of AMR burden and deaths were in sub-Saharan Africa (Kariuki et al., 2022; Murray et al., 2022). The analysis reported that sub-Saharan Africa had the highest all-age death rate that was caused by and associated with AMR, but infections caused by AMR percentages were lower comparatively (Murray et al., 2022). The high burden of AMR was attributable to both resistance and presence of critical infections that are high in this region, such as lower respiratory tract, bloodstream and intra-abdominal infections (Vos et al., 2020; Murray et al., 2022). In this region, it was noted that leading resistant pathogens were different from high-income regions. *Streptococcus pneumoniae* infections lead to 15.9% of deaths and are linked with 19% of deaths. *Klebsiella pneumoniae* infections lead to 19.9% of deaths and linked with 17.5% of deaths (Murray et al., 2022; Sartorius et al., 2024). Meanwhile, the presence of methicillin-resistant *Staphylococcus aureus* was less than 5% in sub-Saharan Africa, along with Europe (Murray et al., 2022).

In South Africa, the AMR surveillance system for human infections is a collaboration between public and private sector laboratory services. This allows for a widespread view of AMR in bloodstream infections in South Africa (National Department of Health, 2022). Bloodstream pathogens monitored are *Enterococcus faecalis* and *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species and *Escherichia coli*. In 2020, *K. pneumoniae* was the most frequent organism isolated from patients in the public and private sectors. This was followed by *S. aureus*, *E. coli*, *P. aeruginosa* and *A. baumannii*. In 2020, *E. faecalis* and *E. faecium* bloodstream infections were resistant to vancomycin in 1.1% and 1.3% of isolates, respectively. *Staphylococcus aureus* bloodstream infections saw 17% of isolates non-susceptible to cloxacillin. In bloodstream infections caused by *K. pneumoniae*, 70% of isolates were non-susceptible to third generation cephalosporins and 40% of isolates were non-susceptible to first generation carbapenems. *Acinetobacter baumannii* bloodstream infections resulted in 80% of isolates resistant to carbapenems. In *P. aeruginosa* isolates, 33% were non-susceptible to carbapenems and 17% were non-susceptible to third and fourth generation cephalosporins and piperacillin-tazobactam. In *E. coli* isolates, 25% were non-susceptible to third generation cephalosporins and 33% were non-susceptible to ciprofloxacin. Similar patterns of non-susceptibility have been reported previously, but a few notable increases have occurred since (Perovic et al., 2018; Ismail et al., 2019).

From 2016 to 2020, *K. pneumoniae* pathogens demonstrated increasing resistance to key antibiotics, including a rise in carbapenem-resistant isolates, notably those resistant to ertapenem, from 8% to 25% (Ismail et al., 2019; National Department of Health, 2022). *Escherichia coli* exhibited an increase in quinolone non-susceptibility from 28% to 32% (Ismail et al., 2019; National Department of Health, 2022). This increase is troubling as quinolones are commonly prescribed for empiric treatment of urinary tract infections (UTIs). *Acinetobacter baumannii* and *Pseudomonas aeruginosa* have heightened resistance to first-line antibiotics, with limited, challenging alternatives like colistin and tigecycline available in South Africa (National Department of Health, 2022). Methicillin-resistant *S. aureus* (MRSA) rates have somewhat decreased and vancomycin resistance remains unreported in South Africa (National Department of Health, 2022). Substantial resistance issues, however, are present in *Enterococcus* species, with *E. faecium* notably displaying a high ampicillin resistance rate. A growth in vancomycin resistance in *E. faecium* presents a rising challenge, especially given the limited alternative treatments available in public healthcare (National Department of Health, 2022). In 2020, 1% of *Streptococcus pneumoniae* isolates were resistant to third generation cephalosporins and 3% had intermediate susceptibility, 4% were resistant to penicillin and 27% were resistant to trimethoprim-sulfamethoxazole (National Department of Health, 2022). The reported data highlights the escalating issue of antibiotic resistance in South Africa. The rise of resistance to first-line antibiotics and, in some cases, last-line antibiotics complicates the management of these infections and may potentially lead to increased morbidity and mortality rates.

Growth of antibacterial resistance is not the only concern in South Africa. Fungal infections are prevalent in South Africa mostly due to the syndemics of HIV/AIDS and TB, and malnourishment due to poverty, leading to immunosuppression and advertently resulting in an estimated 7.1% of population falling ill to opportunistic fungal diseases yearly. *Candida* is recognised as a common fungal infection in South Africa (van Schalkwyk et al., 2019). Antifungal resistance is increasing rapidly, demonstrated by Chibabhai's study (2020) in a tertiary hospital, where the data revealed that the proportion of azole-resistant candidemia cases increased from 39.6% to 69.5% between 2016 and 2020. Further antifungal susceptibility results revealed 0.2% *Candida albicans* and 47.2% non-*albicans* isolates were triazoles resistant, 0.2% *C. albicans* and 0.9% non-*albicans* were amphotericin resistant, 0.3% *C. albicans* and 6.6% non-*albicans* isolates were echinocandins resistant, and 2.5% *C. albicans* and 4.5% non-*albicans* isolates were flucytosine resistant (Chibabhai, 2022). Fourteen isolates were classified as MDR which were *Candida auris, Candida parapsilosis* and *Pichia kudriavzevii* (Chibabhai, 2022). This is concerning as *C. auris* is associated with nosocomial transmission and often encountered in private intensive care settings. In a national laboratory surveillance program from 2016 to 2017, majority of *C. auris* isolates were resistant to fluconazole and a smaller fraction showed amphotericin B or echinocandins resistance (Maphanga et al., 2021). In another study conducted in another public tertiary hospital revealed resistance to fluconazole in *C. albicans, Candida tropicalis* and *Candida krusei* isolates and found multi-drug resistance in *C. albicans, Candida glabrata* and *C. tropicalis isolates* (Mnge et al., 2017). It is also important to note that previous antibiotic exposure is a risk factor for fluconazole resistant bloodstream infections (Ben-Ami et al., 2012; Chibabhai, 2022).

The reported data highlights a crucial need for robust AMS and enhanced surveillance to navigate the growing issue of AMR. Considering the limited treatment options in South Africa's public healthcare systems, thorough research and a collaborated public health goal to manage and mitigate the impact of AMR is critical.

2.2 Policies to reform AMR

In the face of the growing global challenge of AMR, significant strides have been made in understanding and managing this critical public health issue. The recognition of AMR's consequences has led to international discussions and collaborative efforts, leading to the development of strategic plans and surveillance systems (Laxminarayan et al., 2020). In May 2015, the Global Action Plan (GAP) on AMR was adopted by the 68th World Health Assembly (World Health Organization, 2015a). This meant acknowledgement, by the member states, of the AMR global threat posed to human health and proposed detailed actions to combat this threat (World Health Organization, 2015a; Laxminarayan et al., 2020). Following this, the United Nations General Assembly emphasised the need for global co-ordinated action and a One Health Approach (Anderson et al., 2019). This approach is designed to be a holistic and multi-sectoral approach which includes ensuring continuous action in preventing and treating infectious diseases by providing safe, effective and quality-assured antimicrobials and ensuring responsible use (World Health Organization, 2015a; Iwu and Patrick, 2021). The five strategic objectives set to achieve the goal are outlined below in Figure 1. The WHO’s GAP mandates the establishment of national action plans with mutual partnerships to fast track management of AMR. By 2018, of the 194 WHO member states, only 93 have national action plans (Laxminarayan et al., 2020).

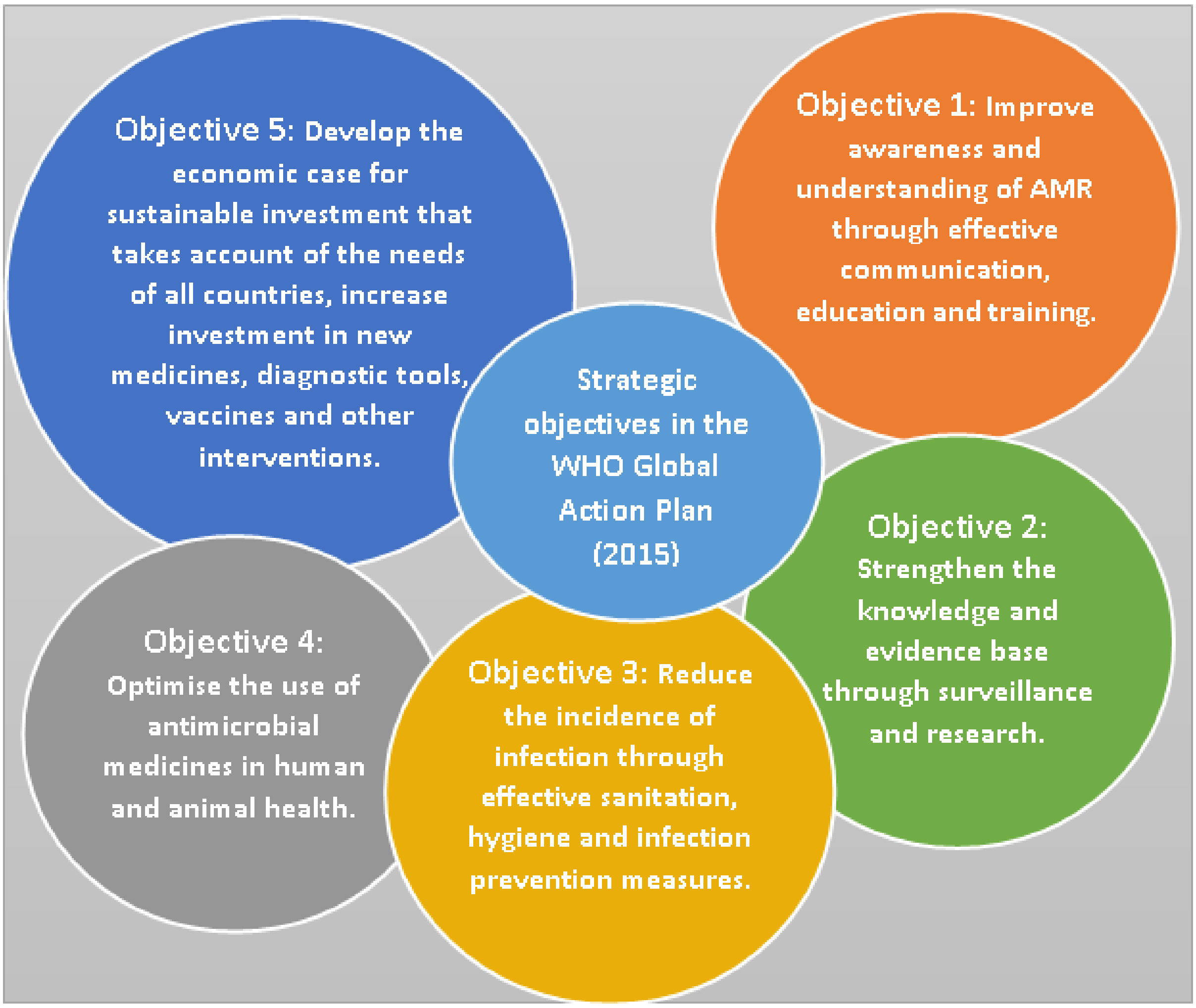

Figure 1: Five strategic objectives outlined in the WHO GAP.

Antimicrobial stewardship covers objective two, four and five of the GAP (Akpan et al., 2020). The GAP outlines that research into sufficient ASPs, optimisation of antimicrobials in both human and animals, and the importance of AMS for newly developed antimicrobials (World Health Organization, 2015a). According to Dellit et al. (2007) the primary goal of ASPs is to reduce AMR while improving clinical outcomes. Along with the WHO, other international, national and professional organisations have advocated the use of ASP to improve antimicrobial use as seen in Appendix D (World Health Organization, 2015a; Barlam et al., 2016; de With et al., 2016). There is no globally standardised framework for ASP management and regulation, however, international policies and guidelines developed by various countries and academic publications have made general recommendations that focus on consensus-based interventions (Dyar et al., 2017a; Van Dijck et al., 2018; Pulcini et al., 2019). The success of the ASP requires strong commitment from senior hospital management leadership, accountability and responsibilities (Centers for Disease Control and Prevention, 2019b; Pulcini et al., 2019). Guidelines for institutional ASPs, therefore, recommend the development of a multidisciplinary team/committee that includes an infectious disease specialist or a microbiologist and a pharmacist with infectious diseases education (Dellit et al., 2007; Majumder et al., 2020). Their core responsibility is to ensure judicious use of antimicrobials. In ASPs, successes are driven with the inclusion of Infection Prevention and Control (IPC) Programmes because the individual aspects of an IPC programme cannot be performed separately (Majumder et al., 2020). Common principles raised, in the ASP guidelines globally, are leadership, accountability, education, monitoring and local antibiogram implementation. A multidisciplinary team should be established and an organisational infrastructure present (Fishman et al., 2012). Actionable processes include preauthorisation of prescriptions and resistance surveillance, and interventions are determined by institutional guidelines and policies. Other types of stewardship interventions include intravenous or oral conversion, intravenous batching, therapeutic substitutions, antibiotic timeout and antimicrobial cycling (Majumder et al., 2020; Tinker et al., 2021).

Before the issue of AMR formed part of the international agenda, individual countries saw their own programmes and guidelines to promote rational use of antimicrobials. In 2007, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) published guidelines on the development of ASPs (Dellit et al., 2007). In 2009, the CDC initiated an educational initiative in the USA to promote the prudent utilisation of antibiotics within acute-healthcare settings. This effort was further reinforced in 2013 when the CDC implemented improving antibiotic usage as a strategic approach to address the issue of AMR (Centers for Disease Control and Prevention, 2017; Davey et al., 2017; Majumder et al., 2020). Other governments, policy makers and researchers tried to draft recommendations for optimal practice to promote AMS initiatives (Charani and Holmes, 2013). These include: antimicrobial self-assessment toolkit and Start Smart – Then Focus, United Kingdom, 2010 and 2012 respectively and a policy statement on AMS by the SHEA, IDSA and the Paediatric Infectious Diseases Society (PIDS), USA 2012 (Fishman et al., 2012). In 2017, the USA government urged that all hospitals must have ASPs in their organisational mandates (Joint

Commission on Hospital Accreditation, 2016). In Europe, many countries implemented ASPs nationally or regionally to improve cost-efficiency, raise awareness of rational antibiotic use, facilitate monitoring and surveillance and provide feedback on prescribing patterns (Oberjé et al., 2017; Majumder et al., 2020). In France, mandatory hospital accreditation includes a composite indicator that assesses both structure and process measures for ASPs within facilities. One structural measure sets a target number of full-time equivalents for infection specialists, pharmacists and microbiologists based on the number of hospital beds. This target was determined solely from expert opinion (Le Coz et al., 2016; Dyar et al., 2017b).

The WHO has also launched the Global Antimicrobial Resistance Surveillance System (GLASS) in October, 2015 as a homogenous approach to AMR data collection, analysis, and distribution by country, assessing the validity of each country's existing or newly developed national AMR surveillance systems (World Health Organization, 2015b). The goal is to combine epidemiological, clinical, and population-level data compared to laboratory data only. In 2017, the WHO Essential Medicine List classified commonly used antibiotics into three groups: Access, Watch and Reserve (World Health Organization, 2017). This provides a tool to support antibiotic monitoring and AMS activities by providing recommendations on when to use the antibiotics in each category for specific infectious syndromes (World Health Organization, 2017). This tool supports antimicrobial optimisation and surveillance (Majumder et al., 2020).

In 2019, the WHO published an ASP toolkit for LMICs. It highlights the significance of understanding the local context when developing and implementing ASPs (World Health Organization, 2019b; Majumder et al., 2020). It is recognised to address AMR drivers in LMICs due to the lack of adequate laboratory infrastructure for microbiological and susceptibility testing, insufficient regulations and ease of antibiotic acquisition, poor sanitation and hygiene, neglected healthcare facilities and inadequate access to second-line or third-line, and quality-assured antibiotics (Cox et al., 2017; Murray et al., 2022). Recommendations include community-based programmes for infection prevention and control, where clean water and sanitation infrastructure are underdeveloped or ill-maintained, and address AMS barriers, such as building necessary foundations to reach the goal of minimising the irrational use of antibiotics (Pierce et al., 2020; Murray et al., 2022; Shamas et al., 2023). This highlights the significance of robust national action plans and laboratory infrastructure to improve surveillance of AMR and management of individual patients and combat this threat to human health in LMICs (Pierce et al., 2020; Murray et al., 2022).

Amidst the worldwide initiatives to combat AMR with ASPs, South Africa also embarked on strategic measures to confront this urgent issue. In 2011, the Global Antimicrobial Resistance Partnership conducted a situational analysis of AMR in humans and animals in South Africa. This led to the formation of the South African Antibiotic Stewardship Programme (SAASP) at the Annual Conference of the Federation of Infectious Diseases of Southern Africa in February 2012 (Govender and Reubenson, 2018; National Department of Health, 2019a). The SAASP was initiated to advocate strengthening AMS in both South African public and private healthcare facilities. It functions in combining in partnership with the NDoH and other stakeholders in the private healthcare sector. The SAASP has developed a standardised national guideline for antibiotic prescriptions, combining established national STGs and other evidence-based interventions (Govender and Reubenson, 2018).

The NDoH has recognised the threat of AMR and the South African AMR National Strategy Framework 2014-2024 was launched in October 2014 and was followed by the implementation plan in 2015 (National Department of Health, 2013, 2015). This framework is a comprehensive approach that includes accountabilities, roles and responsibilities aimed to manage and tackle AMR (National Department of Health, 2013, 2015; Chetty et al., 2019). The national strategic framework was updated in 2018 to strengthen the animal and environmental health aspects of the strategy (Cox et al., 2017; Departments of Health and Agriculture, Forestry and Fisheries, 2018). In November 2018, the NDoH released guidelines for the prevention and containment AMR in South African Hospitals (National Department of Health, 2018). These guidelines were established to support the AMR Strategy Framework and the Guidelines on Implementation of the Antimicrobial Strategy in South Africa. The key components of AMS outlined in these guidelines are: leadership structures (Hospital AMS Committee and AMS team), facility-level interventions, patient-level interventions and monitoring and evaluation of AMS activities and progress (National Department of Health, 2018). Facility-level interventions include applying local guidelines for antimicrobial prescribing, pre-prescription authorisation and prospective audit and feedback. Patient level interventions include assessing whether the patient needs an antimicrobial, if the chosen antimicrobial is appropriate, if it is the appropriate administration and daily review of the need for the antimicrobial. Under the National Institute for

Communicable Diseases (NICD) in South Africa, the GLASS utilises three surveillance programmes to report relevant data. These include the Group for Enteric, Respiratory, and Meningeal Disease Surveillance in South Africa laboratory-based surveillance, NICD sentinel periodic surveillance for sexually transmitted infections (STIs) and the National AMR routine electronic surveillance. There are 737 surveillance sites participating in the national surveillance system consisting of 535 hospitals, 200 outpatient facilities 2 in-outpatient facilities (World Health Organization, 2021b).

Although, South Africa has made progress in AMS policies and guidelines establishment, the compliance to these remains low. A recent study in 26 healthcare facilities in South Africa revealed 59.5% average compliance to the South African AMR national strategic framework (Chetty, 2021; Engler et al., 2021b). National central hospitals had the highest compliance of 73.5%, with referral hospitals complying with 66.9% and the lowest compliance of 38% observed in community health centres (Engler et al., 2021b). Out of 26 healthcare facilities, only five had a compliance greater than 80% and seven had a compliance of less than 50% (Engler et al., 2021b). A recent cross-sectional situational analysis of AMS activities in the KwaZulu-Natal public sector hospital facilities revealed similar results (Chetty et al., 2022). A total of 75% of hospitals had an AMS committee, 47% had a formal written statement of support from leadership and only 7% had financial support budgeted. Regarding infectious diseases specialists, only 5% had an on-site infectious disease physician and 37% had on-site or off-site support from a clinical microbiologist. It was also noted that the individual ASP were at different levels of functioning. Common challenges noted were suboptimal hospital management support, and lack of financial, information technology, microbiology and infectious diseases specialist support (Engler et al., 2021a; Chetty et al., 2022; Scheepers et al., 2023). Time and human resource shortages (such as lack of clinician, pharmacists, nurses and microbiologists) were other barriers that hindered the facilities' ability to successfully operate ASPs (Chetty et al., 2022; Scheepers et al., 2023).

Published literature indicates that South Africa has made great breakthroughs in AMS implementation compared to other African countries (Akpan et al., 2020; Chetty, 2021). A scoping review on AMS in South Africa by Chetty et al. (2019), observed that many hospitals across the country were involved in some sort of AMS activity, including the public and private healthcare sectors. The authors argue, however, most of these interventions were basic quality improvement projects (Chetty et al., 2019; Chetty, 2021). In the private healthcare sector, hospital groups have the capacity and resources to implement ASPs across their facilities (Boyles et al., 2013; Scheepers et al., 2023). The public healthcare sector, in contrast, has many challenges and ASPs have only been successfully carried out in a few hospitals (Junaid et al., 2018; Engler et al., 2021a). Unlike resource rich countries, South African public sector facilities have to use limited resources and provide a basic service, resulting in only rudimentary AMS activities (Chetty et al., 2019; Pulcini et al., 2019; Kakkar et al., 2020). Improvements needed in public healthcare sector include ongoing funding and sufficient human resources to sustain ASPs in these facilities. To ensure further sustainability, AMS interventions should be accompanied with education and ongoing audits (Chetty, 2021; Scheepers et al., 2023). The only way to boost future AMS progression in South Africa is the purposeful investment in finance, staff, time, information technology and resources from all levels of governance and management (Chetty, 2021; Engler et al., 2021a).

2.3 Role of Pharmacists in AMS Programmes

Pharmacists are essential in the worldwide effort to combat AMR by promoting the rational and optimal use of antimicrobials (Dyar et al., 2017b). This corresponds to one of the five strategic objectives of the GAP mentioned above. There is a misconception that AMS activities need to be directed by medical microbiology and infectious disease specialists, yet these persons are not consistently available in all hospitals (Charani and Holmes, 2013). Other healthcare professional and specialities, such as pharmacists, can establish initiatives and lead ASPs. With the input from specialists, these programmes can positively influence antimicrobial prescribing and infection management (Charani and Holmes, 2013; Cantudo-Cuenca et al., 2022).

An article by Lim et al. (2022) examined position statements of pharmacy professional organisations to understand pharmacy’s role in optimising antimicrobial use. The overall key themes are summarised in Table 1 below. The position statements from these professional bodies emphasise that pharmacists are essential in AMS. This is due to their deep understanding of antimicrobials, their expertise in pharmacokinetics (how the body affects a drug), pharmacodynamics (how the drug affects the body), and pharmacoeconomics (the cost-effectiveness of different drugs), their understanding of the impact of antimicrobials on treatment and ensuring that these medicines are used correctly to maximise benefit and minimise harm (Canadian Society of Hospital Pharmacists, 2014).

Table 1: Key themes of position statements made on pharmacists' role in optimising antimicrobial use.

Pharmacists' role in optimising antimicrobial use			
Rationale for pharmacists' involvement in AMS	**Characterisation of pharmacists' AMS role**	**Perceived impact of pharmacist's involvement in AMS**	**Perceived enablers supporting pharmacists' AMS involvement**
- Technical medication knowledge. - Clinical knowledge of medicines' pharmacokinetic, pharmacodynamics and pharmacoeconomic properties. - Knowledge of antimicrobials' impact on treatment. - Ability to promote safe and effective use of medicines. - Within scope of practice to treat common and minor ailments. - Reduce burden of other healthcare services by offering over-the-counter medicines, thus reducing "antibiotic-seeking" behaviour. - Accessible to public and known as "first port of call" for patients and last healthcare worker to talk to before starting treatment.	- Advisors and educators, offering technical advice for antimicrobial optimisation and offering patients advice on self-care and management of minor ailments. - Operating within a multidisciplinary team. - Promotor of infection control and prevention practices, such as hand hygiene and immunisation programmes. - Leadership and governance positions at health system and health service levels, overseeing AMS programmes and initiatives. - AMS consultant positions. - Gatekeepers of antimicrobial use, offering point-of-care testing and making informed decisions regarding referral to a prescriber. - Researcher in drug discovery and design, and AMR. - Safe disposer of leftover, unused or expired antimicrobials.	- Optimising antimicrobial prescribing. - Supporting improved health service utilisation. - Supporting treatment of minor ailments. - Improving patient awareness and understanding of AMR. - Positive contribution to antimicrobial research and development in academia and industry.	- Government support and advocacy, carrying out educational campaigns to promote pharmacists' involvement in AMS, related policies and guidelines. - Government and industry, supporting research and development of novel antimicrobials and safe disposal of antimicrobials. - Pharmacist specialist training and education in AMS and infectious diseases, with access to clinical information and technology to allow for surveillance and monitoring activities.

Pharmacists are often easily more accessible and assist in treating common and minor ailments which can reduce unnecessary prescriptions for antimicrobials (Royal Pharmaceutical Society, 2017; Pharmaceutical Group of European Union, 2020). Pharmacists play a multifaceted role in AMS because they are positioned to provide technical advice for antimicrobial optimisation and work collaboratively with other healthcare professionals (American Society of Health-System Pharmacists, 2010; International Pharmaceutical Federation, 2015). Pharmacists' involvement in AMS is believed to have several positive impacts. They ensure the right antimicrobials are used for the right conditions, assist in the efficient use of healthcare resources, educate patients about the risks of AMR and play a vital role in antimicrobial research, development and supply. To summarise pharmacists are crucial in the fight against AMR, contributing through their expertise in medication, patient education, research and policy implementation (Lim et al., 2022). Their involvement is supported and enhanced by governmental and industrial efforts to promote and facilitate their role in AMS. Research has consistently demonstrated this globally. In 2015, an international cross-sectional survey of ASP in hospitals observed that antimicrobial or infectious disease pharmacists are the main manpower in Asia, Europe, North America and Oceania (Howard et al., 2015).

Research has demonstrated the impact of pharmacist-led ASPs (Khanina et al., 2021; Wang et al., 2022; Xu et al., 2022). Pharmacists have successfully led education-based AMS interventions to enhance antimicrobial prescribing (Monmaturapoj et al., 2021). These interventions have led to improved antimicrobial prescribing behaviour and competency. especially if conducted with face-to-face communication with prescribers. Combining interventions, such as audit and feedback, have shown better compliance to AMS policies. In a recent meta-analysis on the evaluation of inappropriate antibiotic prescribing and management through pharmacist-led ASPs, the authors observed in 14 published articles where pharmacist-led AMS programmes showed positive impact in reducing inappropriate prescribing of antimicrobials employing different strategies (Mahmood et al., 2022). Another meta-analysis of 28 studies evaluating the impact of pharmacist-led AMS programmes observed ten out of 13 studies reported less mortality rates, six studies reported treatment cost reduction, 11 of 12 studies reported length of hospital stay reduction, eight studies reported reduced return rate to hospital within 30 days and eight studies reported a reduction in treatment duration (Mahmood et al., 2021).

Published literature on the influence of pharmacist-led ASPs in sub-Saharan Africa has demonstrated that pharmacists in these countries were capable of developing and directing AMS programmes similar to resource-rich countries (Otieno et al., 2022). In these studies, pharmacists improved guideline compliance of antibiotic prescribing and altered prescriber behaviours by mentoring, educating and training healthcare teams, both formally and informally (Abubakar et al., 2019; Gebretekle et al., 2020; Sneddon et al., 2020; Kerr et al., 2021). Audit and feedback was another strategy employed where antibiotic prescription compliance was assessed with current guidelines and feedback was given to prescribers individually or in meetings (Abubakar et al., 2019; Momanyi et al., 2019; Gebretekle et al., 2020; Sneddon et al., 2020; Kerr et al., 2021). Pharmacists also actively participated in developing protocols with other healthcare professionals (Abubakar et al., 2019; Gebretekle et al., 2020; Sneddon et al., 2020; Kerr et al., 2021). These pharmacists carried out ward rounds where assessments on the appropriateness of antibiotic treatments were conducted and prompt oral or written feedback was made to prescribers. Typical interventions include stopping of antibiotics due to lack of indication, de-escalation, optimisation of antibiotic dosages and intravenous to oral switch (Abubakar et al., 2019; Gebretekle et al., 2020; Kerr et al., 2021). The successful impact of pharmacist-led AMS programmes demonstrated through various studies and meta-analyses, is mirrored in South Africa's healthcare system, where pharmacists' roles in AMS are increasingly recognised and integrated into hospital guidelines.

Pharmacists' role in AMS in South Africa has gained momentum and is recognised for its impact in the healthcare settings. In the guidelines for the prevention and containment of AMR in South African Hospitals, it states that the hospital AMS committee should include a chief pharmacist and that the AMS team must include a pharmacist (National Department of Health, 2018). The role of the pharmacist in the AMS team is outlined in Figure 2 below. The roles described mirror many of the roles stated in international guidelines. Common themes observed are medication advisory, education, member of the AMS team, providing audit and feedback. The recognised duties of pharmacists include verifying the correct use of antimicrobials, documenting patient allergies and medication history, evaluating the suitability of antimicrobial prescriptions and facilitating prompt medication access (National Department of Health, 2018; Centers for Disease Control and Prevention, 2019b; Australian Commission on Safety and Quality in Health Care, 2023). They are also expected to reconcile all patient medications, interpreting initial microbiology results for empiric antimicrobial therapy adjustment, and monitoring antimicrobial dosing in line with pharmacokinetic and pharmacodynamics principles, including therapeutic drug monitoring (National Department of Health, 2018; Centers for Disease Control and Prevention, 2019b; Australian Commission on Safety and Quality in Health Care, 2023). Other key duties also encompass halting antimicrobial treatment when no longer necessary, conducting pharmacovigilance, reviewing and adjusting treatment based on final culture reports and advocating for the switch from intravenous to oral antimicrobials (National Department of Health, 2018; Australian Commission on Safety and Quality in Health Care, 2023). Other expectations are ensuring the compatibility of intravenous antimicrobials, determining the correct treatment duration, auditing antimicrobial use, providing feedback, advising on AMS advancements, educating patients about antimicrobials, and implementing infection prevention and control practices (National Department of Health, 2018; World Health Organization, 2019b). These varied tasks allow for accurate antimicrobial application, continuous supervision, patient education and adherence to guidelines to effectively manage and curb AMR. South African public facilities lack the human resources, specialist pharmacists in this case, to carry out ASPs. Nevertheless, the pharmacists that are available in both public and private facilities are being utilised in ASPs and published literature has shown optimistic results.

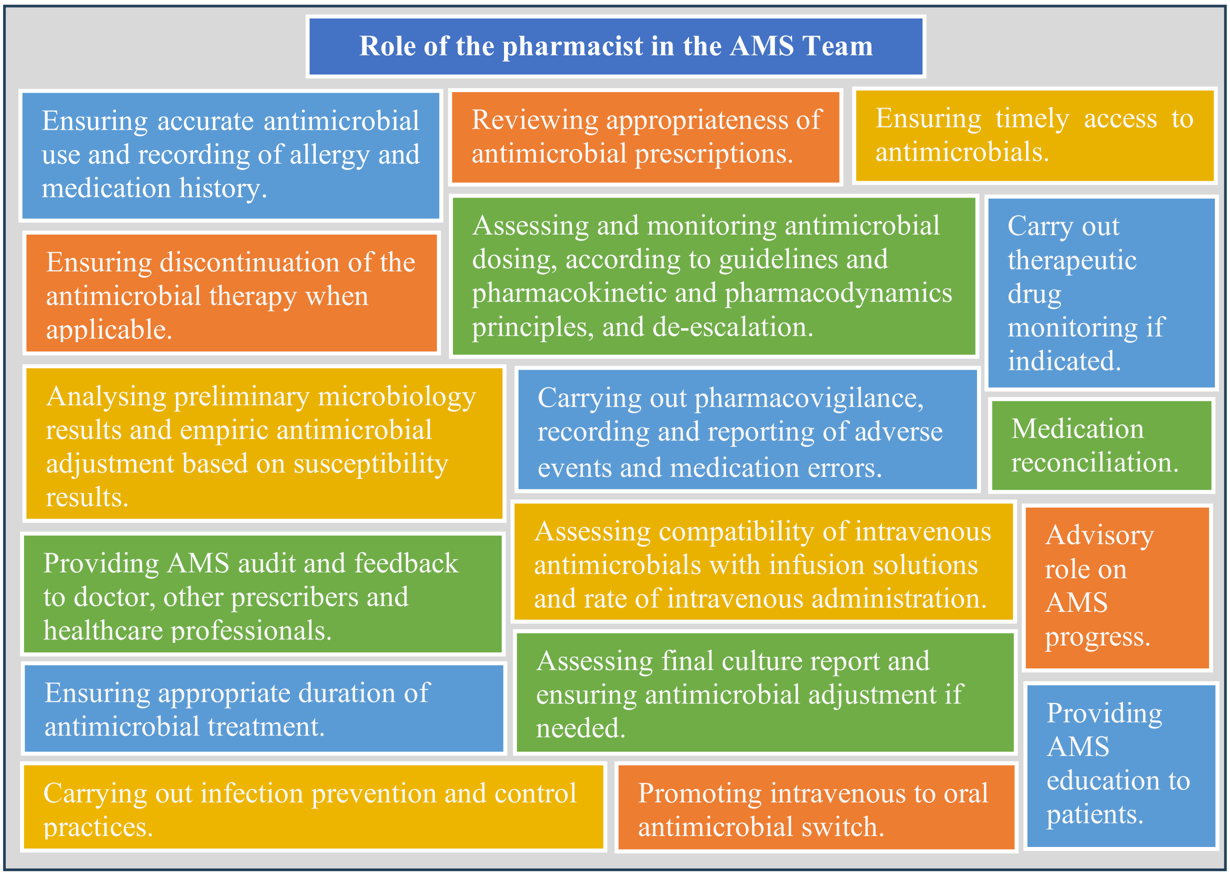

Figure 2: Summary of the role of the pharmacist in the AMS team as per the guidelines for the prevention and containment of AMR in South African hospitals.

Research in South African hospitals support the role of pharmacists in AMS. Pharmacist-led interventions were associated with improved compliance with antibiotic guidelines, appropriateness of prescribing, reduction in antibiotic use and cost savings. A recent study demonstrated that pharmacist-driven, AMS implementation of community-acquired pneumonia (CAP) guidelines in both public- and private-sector hospitals showed an overall improvement in both diagnostic (radiological investigations, microbiology cultures and admission criteria) and antibiotic measures (drug choice, dose, treatment and intravenous to oral switch) (van den Bergh et al., 2020). Another recent study of a pharmacist-driven introduction of antibiotic prescription charts in paediatric medical ward of a public hospital demonstrated decrease antibiotic utilisation and increase in microbial culture and sensitivity testing (Salau et al., 2023). A study reported that a pharmacist-driven AMS programme across 47 private hospitals reduced antibiotic defined daily dose (DDD) per 100 patient days of 18.1% (Brink et al., 2016). Another study that implemented pharmacist-led interventions resulted in a decrease of surgical site infection rate and reduced antibiotic use (Brink et al., 2016). South African studies have also shown that pharmacists participating in ward rounds have improved APS by overseeing issues like overlapping antimicrobial spectrum activity, polypharmacy, inappropriate dosages and treatment durations and irrational prescribing (Ramsamy et al., 2019; Chetty et al., 2022). Another study across 33 private hospitals demonstrated pharmacist-led AMS interventions led to sustained improvement in hang-time compliance (time taken from prescribed antibiotic order to actual intravenous administration) ensuing timely administration of antimicrobials (Messina et al., 2015). A study implemented a multidisciplinary team that led to cost saving and reduced antibiotic consumption, but non-significant change in mortality and 30-days readmission rate (Boyles et al., 2017). These studies that had pharmacist-led ASPs indicated that pharmacists are a valuable resource in a healthcare setting that has limited specialist resources (Akpan et al., 2020). Junaid et al. (2018), however, showed no change in antibiotic consumption with the ASP, but attributed this to the programme's early stages in establishment. The programme did succeed in boosting ward rounds, tracking and reporting of AMS process measures (Junaid et al., 2018). Although, South Africa, like many countries in Africa, face its own challenges, these studies present the successes of ASP in hospital settings.

2.4 Pharmacist education and training in South Africa

Barriers to South African pharmacists' activities in ASP stems from their fundamental education. The South African NDoH recommends that AMS be taught in undergraduate pharmacy curricula, however, the specialising of pharmacists in infectious diseases and AMS is not yet standardised and formalised (Schellack et al., 2018; Chetty and Leigh-de Rapper, 2023). A quantitative exploratory study surveying clinically practicing pharmacists in public and private healthcare sectors in South Africa emphasised this. While these pharmacists expressed good attitudes, knowledge and perceptions towards AMS, they indicated that knowledge on AMS was likely to be obtained at conferences, workshops, postgraduate programmes and short courses and less so in undergraduate programmes, although acknowledged some form of AMS training (Chetty and Leigh-de Rapper, 2023). The pharmacists also noted that their undergraduate education was inadequate in preparing them for their AMS responsibilities and it would be beneficial to introduce a comprehensive course in AMS and infectious diseases (Chetty and Leigh-de Rapper, 2023). There is limited focus of AMS in undergraduate training and postgraduate training is needed to fill in the knowledge gaps. Pharmacists in South Africa feel that the lack of education, training and recognition of roles are major limits to their participation in the AMS multidisciplinary team (Manyama et al., 2020). It is noted that not all pharmacy schools in South African universities offer a postgraduate clinical pharmacy programme, limiting the spaces available and logistic accessibility to these programmes. The South African Pharmacy Council (SAPC) does partially acknowledge the role and scope of practice of a ward pharmacist in South Africa, but not as a clinical pharmacist. The speciality was recognised by SAPC through the Board Notice 152 of 2014, but nothing has changed with regards to registering as a clinical pharmacist in South Africa. This discourages pharmacists to spend their time and financial resources into this formal training (Bronkhorst et al., 2020). Pharmacists are, therefore, registered as a pharmacist regardless of obtaining a postgraduate degree in clinical pharmacy. The consequence of this lack of differentiation is that pharmacists with Bachelor of Pharmacy and those with a Master of Pharmacy are both performing clinical functions and involved in AMS (Bronkhorst et al., 2020; Khan et al., 2020). It is argued that pharmacists that have a postgraduate degree in clinical pharmacy should receive the title of a specialist pharmacist with a clear definition of roles and responsibilities (Bronkhorst et al., 2020). This will help standardise the postgraduate training, as they are not currently regulated on scope or structure.

2.5 Areas of concern in South African healthcare

Published data indicates that LMICs utilised more antibiotics between the years 2000 – 2015 compared to previous years and resulted in a 65% increase in global antibiotic consumption

(Klein et al., 2018). Studies indicate that antibiotics are inappropriately used in private and public healthcare facilities in African countries (Gasson et al., 2018; Labi et al., 2018; Umar et al., 2018). A cross-sectional, retrospective study conducted in a Mozambican hospital reported that 97.5% of hospitalised paediatric patients were prescribed antibiotics, however, 36.5% of these prescriptions had errors such as inappropriate dosage, duration of treatment and duplicate spectrum of activity (Xavier et al., 2022). Another study conducted in a Zambian large teaching hospital reported that 67% of antimicrobial orders were inappropriately prescribed due to incorrect doses and/or frequency based on recorded indication and/or renal function, and the duplicate or inadequate spectrum of activity (Masich et al., 2020). A point prevalence survey in six Tanzanian hospitals reported that approximately 62.3% of inpatients were prescribed antibiotics, however the majority of these were empirical and only 0.3% were targeted as per the culture and antimicrobial susceptibility results (Seni et al., 2020). Inappropriately prescribed antibiotics is not the only issue faced in sub-Saharan African countries because patients are also able to access antibiotics without prescriptions. A literature review of 23 studies from 11 different countries reported, on average, 69% of requests or consultations for antibiotics without a prescription at community drug retail outlets were accepted and provided antibiotics (Belachew et al., 2021). South Africa is also culpable of excessive antibiotic consumption. The South African NDoH reported that according to an international report, South Africa's antibiotic use was 9177 DDD per 1000/population in 2015 (National Department of Health, 2022). In comparison to other BRICS (Brazil, Russia, India, China and South Africa) countries, it was substantially higher. Other BRICS countries reported in 2015: Brazil 6763, Russia 6069, India 4950 and China 3060 DDD per 1000/population (National Department of Health, 2022). Although South Africa's use was the highest in the BRICS countries, it did remain lower than higher income countries such as USA (10298), Canada (7078) and Australia (11088) (National Department of Health, 2022). Import data revealed that between 2018 and 2020 there was a 26.3% increase in human antibiotic imports, equating to 1.7 tons (National Department of Health, 2022).

The South African conventional healthcare system consists of public and private sectors. The public sector is run by provincial government health departments and includes primary, secondary and tertiary health services. These services are provided through various health facilities managed by the provincial departments, all under the supervision of the NDoH (Rwafa-Ponela et al., 2021). Although the minority of South African citizens are covered by a medical scheme and receive private healthcare, the private sector spends more on antibiotics in South Africa compared to the public sector (National Department of Health, 2022).

In the South African NDoH's surveillance report, from 2018 to 2020 the public sector experienced notable shifts in antibiotic usage, with extended-spectrum penicillins emerging as the most commonly used class (National Department of Health, 2022). Extended-spectrum penicillins accounted for 28% of total antibiotics used in 2020 in the public sector. Oral trimethoprim-sulfamethoxazole followed with 13% and metronidazole at 12%. There was an increase in third generation cephalosporins use, from 4% in 2018/2019 to 10% in 2020. The broad-spectrum penicillin usage is higher compared to other countries because it is 12 % higher than the United Kingdom and 15% higher than Russia, but still 12% lower than the USA. The higher trimethoprim-sulfamethoxazole use is due to the high burden of HIV in South Africa and prophylactic prescribing to prevent *Pneumocystis jirovecci* pneumonia (Suthar et al., 2015). In the public sector, observed reductions in procurement of Access and Watch antibiotics are noted, however, a slight increase in procurement of Reserve antibiotics of 0.31% for 2020. In 2020, 73% of antibiotics procured were in Access group and this is greater than the WHO recommended target of over 60%. It is noted, however, that the public healthcare sector does not have equal access to Watch and Reserve groups of antibiotics. The Ministerial Advisory Committee on AMR of South Africa believes that the use of community Access antibiotics should aim closer to 80% because of the current bacterial resistance patterns of common pathogens causing community-acquired infections (National Department of Health, 2022). This detailed analysis of antibiotic usage and procurement trends provides a crucial context for understanding the findings from studies in different settings of the public healthcare sector on antimicrobial utilisation in South Africa.

2.5.1 Hospital settings

A recent point prevalence survey collected data on antimicrobial usage trends among 18 public sector hospitals in South Africa and reported that there was a 90.2% overall compliance with the current South African STGs/essential drug list (EDL) for all the antimicrobials prescribed (Skosana et al., 2021). Prescribing outside the STGs/EDL was mostly observed in surgical wards followed by medical wards (Skosana et al., 2021). Another study in a public tertiary hospital in Gauteng reported only 55.2% compliance to the STG/EDL for SSTIs in the surgical wards (Makwela et al., 2023). Non-compliance was due to inappropriate antimicrobial choices, inappropriate dosing intervals and duration, and the lack of antibiotic de-escalation following the release of microbiology test results (Makwela et al., 2023). Disappointingly, culture and antimicrobial susceptibility testing were only conducted in 40.3% of cases in the study (Makwela et al., 2023). A cross-sectional survey conducted on doctors, nurses and pharmacists in six public hospitals reported that 73.5% of participants indicated inappropriate antimicrobial use was a major contributor to AMR (Reddy et al., 2023). Other contributors suggested were interruptions to antimicrobial therapy, ineffective IPC practices, inappropriate use of laboratory diagnostic tests, the lack of rapid diagnostic tests and lack of close clinical follow-up (Reddy et al., 2023). A retrospective study conducted on paediatric antibiotic prescriptions in a public hospital in Limpopo reported only 6.9% of cases in which antibiotics were prescribed as per the interpretation of culture and antimicrobial susceptibility results, 66.1% of antibiotic prescriptions were empiric and 69.1% antibiotic prescriptions were in accordance to the Paediatric Hospital STG/EDL (Mabila et al., 2016). Observed reasons for non-adherence was due to inappropriate antibiotic dosages, choices, administration and dosing frequency (Mabila et al., 2016). These studies collectively highlight a significant issue of non-compliance with STGs and inappropriate antibiotic prescribing in South African public hospitals.

2.5.2 Primary healthcare settings

In primary healthcare settings the practitioners are expected to follow the STGs, although, this not always the case (Abahamye, 2016; Hoffman et al., 2017; Hlalo, 2018). Gasson, Blockman and Willems (2018) revealed that over half of the number of patients not provided with a diagnosis, were still prescribed antibiotics. Crichton et al. (2018) found that dual antibiotic cover was the second highest reason for inappropriate prescriptions. A study conducted in a community healthcare centre in Pietermaritzburg assessed whether parents or guardians that accompanied their children (years five and below) with upper respiratory tract infections (URTIs) either expected or influenced physicians or nurses to prescribe antibiotics (Mathibe and Zwane, 2020). The result was that 76% of children that received antibiotics for their URTIs, 67% of parents or guardians did not make requests for them and there was a statistically significant chance ($p < 0.0001$) for receiving antibiotics for URTIs without a request (Mathibe and Zwane, 2020). As mentioned previously, URTIs do not warrant antibiotics and they have no benefit in these conditions (Mathibe and Zwane, 2020; Alabi and Essack, 2022). The findings of this study suggest that the prescribers irrationally prescribe antibiotics, do not adhere to guidelines and are not pressured by patients in the public sector to do so (Mathibe and Zwane, 2020). These findings were similar to another study by Manderson (2020). A qualitative study of observing clinic waiting rooms and patient/provider consultations in public and private healthcare settings. Most of the patients reported that they did not automatically expect to receive antibiotics, but some did have clear intentions of receiving (Manderson, 2020). A qualitative study conducted by van Hecke et al. (2019) explored the perceptions of South African public primary healthcare clinicians about making antibiotic prescribing decisions for two common infection syndromes and experiences with point-of-care tests. Most clinicians felt they were practising according to the STG for common ailments but considered it less urgent than improving management of more serious infections, such as HIV, TB and rheumatic fever. They also mentioned that their treatment decisions were influenced by social determinants of health, such as access to care and perceived patient expectations for antibiotics. One doctor stated that, although, they knew the condition had a viral origin, they would prescribe the antibiotics either because they were elderly, cannot easily access the facility or do not have transport (van Hecke et al., 2019). These considerations for patients were also mentioned in Manderson's study (2020), such as time, feasibility, costs involved and having to take unpaid leave. Clinicians also revealed that patients rarely received follow-up appointments for common infections because the clinics are overcrowded and follow-up in three days to re-assess the patient is not practical, hence, the acquisition of an antibiotic prescription on the first visit (van Hecke et al., 2019).

2.5.3 Emergency departments

The ED is often the initial point of care when patients are brought to the hospital (Almansoori and Parag, 2021). A study conducted in a public regional ED in KwaZulu-Natal assessed the management of patients presenting with diarrhoea (Kudsk-Iversen et al., 2014). The study was conducted over two months and a total of 72 patients were included, of which 58 were HIV-positive. Of the 72 patients, 43 (60%) patients received antibiotics, but only 15 (34.9%) of these patients cultured bacteria in their stool and only 25 (58%) prescriptions followed EDL guidelines. The authors noted that the antibiotic prescription was unrelated to disease severity or possible hospital admission. The findings also revealed that 84% of these patients received only a single dose of antibiotic, which put the patient at greater risk of an untreated infection and resistance development. This is worsened if the patient has HIV and further increases risk of antibiotic-associated colitis caused by *Clostridium difficile* (Byarugaba, 2004; Venkat et al., 2008; Kudsk-Iversen et al., 2014). Overall, the antibiotic treatment of these cases was inconsistent and clearer guidelines for prescribing and management for acute diarrhoea in HIV-positive patients is warranted (Kudsk-Iversen et al., 2014).

Another more recent study conducted in a public regional hospital ED assessed the antibiotic prescribing patterns (Almansoori and Parag, 2021). This was a retrospective review of patient medical records over one month. A total of 1454 patient medical records were included in analysis and only 195 (13.41%) patients received antibiotics. Prescriptions were analyses using EDL 2015 to determine the if the choice of antibiotic was appropriate. The findings revealed a non-significant statistical ($p = 0.654$) relationship between the appropriate and inappropriate prescriptions, 46.2% and 48.2% respectively. The majority of patients received a single antibiotic agent (87.18%), 11.28% received two antibiotic agents and 1.54% received three antibiotics. Amoxicillin/clavulanic acid was the most frequently prescribed antibiotic either as a single agent or in combination with azithromycin, followed by ceftriaxone. The prescribed dosages were correct in 92.8% of cases. This study demonstrated insights into the prescribing frequency of antibiotics in a South African hospital's ED and was not condition specific (Almansoori and Parag, 2021). Although, there was no statistical significance between appropriate and inappropriate choice, it is still concerning that the percentage of the inappropriate antibiotic choices were higher than appropriate.

While these two studies demonstrate inappropriate antibiotic prescribing patterns in the ED, published data is still lacking as this healthcare setting in South Africa is under researched. These studies collectively underscore the need for more robust research and development of interventions to improve adherence to guidelines to optimise antimicrobial use. The gap in research specific to this healthcare setting in South Africa points to an opportunity for future studies to enhance the understanding of antimicrobial prescribing patterns and to improve patient outcomes in emergency care. It is a necessary step towards ensuring better patient care, improving health outcomes, and mitigating the threat of AMR.

2.6 Antimicrobial use and appropriateness in EDs

Emergency departments are placed in a unique position between outpatient and inpatient settings and have a great influence in antimicrobial use and resistance patterns within the community (Bishop, 2016). It is important to understand the antimicrobial use in these settings to determine if AMS interventions are necessary and if they would be beneficial. Published literature, in the last ten years, from various countries has reported the inappropriate use of antimicrobials in EDs. The summaries of the studies are outlined in Appendix E. These countries are from five different continents which emphasises the international scale of the problem.

In the USA, numerous studies have been published on antimicrobial usage and prevalence of appropriateness of antimicrobial prescriptions in ambulatory care settings, such as EDs and outpatient settings which are summarised in Appendix E. The main findings of these studies reveal inconsistencies and often problematic practices in antibiotic or antimicrobial prescribing, such as over-treatment, under-treatment, and non-adherence to established guidelines. Several studies looked at the appropriateness of antimicrobial prescribing for a variety of commonly seen diagnoses in the ED and the results are concerning. Timbrook et al. (2017) reported that only 61% of antimicrobial prescriptions were appropriate. This value was similarly reported by White et al. (2019) where 60% of antibiotic prescriptions were appropriate. Kiel et al. (2020) more recently reported a lower percentage of 43.3% compared to Timbrook et al. (2017) and White et al. (2019) findings. These studies collectively emphasise the need for improved prescribing practices, better adherence to guidelines and the importance of accurate diagnosis and treatment decisions in ambulatory care settings. These patterns are observed in the treatment of conditions of SSTIs, acute respiratory infections, UTIs and others. Haran et al. (2015) focused on cellulitis and abscess diagnoses and revealed that 43% of patients were treated according to treatment guidelines which was significantly greater than 20.1% reported by Kamath et al. (2018) in similar conditions. Prusakowski and Kuehl (2015) found that a significant proportion of discharged patients (range of 71.8% to 75.5%) received antibiotic prescriptions for their abscesses after incision and drainage, which may indicate inappropriate use. Additionally, many patients received multiple antibiotics, which raises concerns about potential overuse (Prusakowski and Kuehl, 2015). Three studies assessed appropriateness of antibiotics for respiratory tract infections and reported varying results. Fleming-Dutra et al. (2016) estimated that 30% of outpatient oral antibiotic prescriptions may have been inappropriate which was similar to the findings of Walsh et al. (2020) who reported that 28.4% of patient encounters received antibiotics, although they were not indicated. Conversely, Wattengel et al. (2019) revealed that 69.2% of patients with CAP received antibiotics regimens incompliant to treatment guidelines. Four studies focused on the appropriateness of antibiotics in UTIs. Maddali et al. (2021) reported only 64% of patients with uncomplicated UTIs received first-line treatment. Patel et al. (2020) found that 87% of patients with an uncomplicated or complicated cystitis received empiric antimicrobial therapy in accordance with guidelines. Patel et al. (2020) also identified that only 57% of patients with pyelonephritis were administered guideline-congruent antimicrobial therapy, which was much greater than the 36.1% reported by Zatorski et al. (2016). Common reasons identified for inappropriate antimicrobial therapy were unsuitable choices, durations and dosages. These studies highlight the inappropriate prescribing practices in these ambulatory care settings, due to overuse and under-treatment of antimicrobials along with variations in compliance with treatment guidelines.

In Europe, two studies were conducted in Spain and two studies in France. The first study in Spain was a retrospective review of paediatric patient medical records from the emergency section of a secondary university general hospital. The use of the antibiotics and appropriateness according to diagnosis were assessed using established guidelines (Guzmán Molina et al., 2014). Of all diagnoses, infections accounted for 65.3% and most diagnosis were URTIs with the common cold being the highest diagnosis. Antibiotics were mostly prescribed for acute otitis media, less in pneumonia and a low rate of antibiotic prescriptions for common cold, bronchitis and bronchiolitis. The authors reported that there was good compliance with the published guidelines in terms of appropriateness and the antibiotic selection for empirical treatment (Guzmán Molina et al., 2014). A more recent study was conducted in a Spanish paediatric ED of a tertiary care hospital that retrospectively reviewed medical records of patients under 16 years old discharged from this facility (García-Moreno et al., 2022). This study had similar results in that 88% of cases, antimicrobial therapy was considered appropriate in every aspect according to published guidelines (indication, selection, dose, dose interval, duration of treatment and route of administration) (García-Moreno et al., 2022). The first study in France was a retrospective monocentric study, in the ED of a teaching hospital (Grenet et al., 2016). The study revealed that 59.9% of cases received inappropriate antibiotic treatments according to guidelines due to no indication for antibiotics (40.7%), inadequate spectrum of activity (19.6%), excessive treatment duration (18.0%) and excessive doses (3.3%). The rates of inadequate prescriptions per condition were 82.3% for ear, nose and throat infections, 71.2% for cutaneous infections, 46.5% for respiratory tract infections and 38.4% for UTIs. Inappropriate prescriptions were mainly associated with amoxicillin/clavulanic acid (39.4%) and fluoroquinolones (31.4%) (Grenet et al., 2016). The second study conducted in France by

Lalande et al. (2018) evaluated the prevalence of medication errors in a paediatric ED of a university hospital and described their characteristics and determinants. Medication errors were present in 30% of antibiotic prescriptions. The errors included posology, antibiotic choice, omission and pharmaceutical form errors (Lalande et al., 2018).

In Asia, published literature is available across different countries on the appropriateness of antimicrobials prescribed in the ED. In the Middle East, one study conducted in Saudi Arabia in one hospital reported that 46.2% of antibiotic prescriptions were inappropriate (Alanazi et al., 2015). The distribution of errors was as follows: 2% selection error, 4.2% frequency error, 21.7% dosage error and 28.6% duration error (Alanazi et al., 2015). It is promising that there was only a 2% selection error, but the suboptimal treatment due to frequency, dosage and duration errors is concerning. Also in the Middle East, a study was conducted in three Lebanese hospitals and found overall there was 32.6% adherence to international guidelines (including conditions for CAP, sepsis, UTIs and SSTIs) (Fahs et al., 2017). The condition with the least adherence to guidelines was CAP at 28.3%. Prescriptions including beta-lactams adhered less to guidelines (Fahs et al., 2017). These studies have very diverse findings, but this may be attributed to the differences of healthcare policies in a LMIC compared to a high-income country. A cross sectional study of an outpatient department in a tertiary medical college hospital was carried in Bangladesh (Ata et al., 2019). The findings showed that from the total of prescriptions in this setting, 46% were antibiotics, only 52.9% of the antibiotics were prescribed from EDL of WHO and 19.7% of injectable antibiotics prescribed which is higher than the WHO recommendation of 10% or less (Ata et al., 2019).

A study in Japan was conducted assessing the misuse of prescribed antimicrobials in discharge prescriptions in the ED of a tertiary medical centre (Tagashira et al., 2019). The study reported that 52.3% of discharge prescriptions showed misuse of antimicrobials (Tagashira et al., 2019). This finding was very close to other findings in Asian countries (Alanazi et al., 2015). Unnecessary antimicrobial prescriptions accounted for 27.5%, inappropriate antimicrobial prescriptions accounted for 21.7% and suboptimal antimicrobial prescription accounted for 3.1% of cases (Tagashira et al., 2019). The authors stated that misuse frequently occurred during late-night visits, and when older physicians and physicians in a surgical subspecialty prescribed the antimicrobials (Tagashira et al., 2019). Two studies in China conducted in paediatric ED and outpatient departments of tertiary care hospitals (Zeng et al., 2017; Wang et al., 2020). Zeng et al. (2017) reported that 62% of paediatric patients during the study period received antibiotics. Antibiotics were prescribed in 80.5% children with a wheezy bronchitis, 87% with tonsillitis and 25% with URTIs. The frequently prescribed antibiotics were cephalosporins (75.3%) and penicillin (22%). Antibiotics prescribed for children with an URTI or tonsillitis was deemed inappropriate and it was over the 20% maximum recommended by the European Surveillance of Antimicrobial Consumption (Adriaenssens et al., 2011; Zeng et al., 2017). The study conducted by Wang et al. (2020) showed similar results. Wang et al. (2020) included 16 tertiary hospitals in their study and antibiotics were prescribed in 36.3% of all encounters and varied across hospitals (from 26.6% to 59.7%). Antibiotics were more frequently prescribed in general hospitals and EDs, compared to specialised children's hospitals and outpatient departments. Third generation cephalosporins were mostly prescribed across all age groups. At least 70% of antibiotic prescriptions were for respiratory tract infection diagnoses.

In Australia, two studies looked at the appropriateness of prescriptions in the EDs of their respective tertiary hospitals and one study conducted a survey for ED doctors in one hospital to assess their prescribing practices compared to published guidelines. The study by Birdsey et al. (2016) looked specifically at mammalian bites and found that there was 61.9% adherence to guidelines. Of the antibiotic prescriptions that were not adherent, 18.7% of cases the antibiotic choice was not according to guidelines, 11.9% of cases required an antibiotic, but did not receive and 7.5% of cases received antibiotics that were not indicated (Birdsey et al., 2016). Denny et al. (2019) conducted a retrospective, observational study in a large, public tertiary ED assessing appropriateness of antibiotic prescribing. During the study period of weeks, 13.6% of all patient presentations involved at least one antibiotic (Denny et al., 2019). From these 62.8% were deemed appropriate, 32.7% were deemed inappropriate and 4.5% were not assessable. There is a pattern seen here that one in three prescriptions in these EDs are inappropriate and these findings suggest an area for AMS interventions in these settings (Birdsey et al., 2016; Denny et al., 2019). The case vignette survey conducted by Clemence et al. (2018) found that 54% of antibiotic choices were optimal according to the National Antimicrobial Prescribing Survey guidelines, 18% of choices were adequate, 16% of choices were suboptimal and 12% were inadequate. The survey looked at specific conditions and the findings showed that 100% of appropriate antibiotic choices were made for uncomplicated UTIs, 77% were made for severe pyelonephritis, 69% were made for severe cellulitis, 42% were made for moderate CAP and

69% were made for sepsis of unknown origin (Clemence et al., 2018). Although, these were hypothetical cases, the choices made by the ED doctors reflected, somewhat, similar appropriateness results to real life circumstances as seen in the Birdsey et al. (2016) and Denny et al. (2019) studies.

In Africa, a number of studies have been conducted in five different countries. Two studies focused on antimicrobial utilisation in outpatient settings. One retrospective observational study set in Liberia, looked at antimicrobial use in the ED in a low-resource setting (Yi et al., 2022). Over a six-month period, 65.3% of assessed ED patient charts had antimicrobials prescribed, totalling 1212 antimicrobial prescriptions, and the conditions associated with the most antimicrobial prescriptions were abdominal infections, malaria, UTIs and sepsis. The average number of antimicrobials per a patient was 1.12 and 35.7% of the patients received more than antimicrobial. The most commonly prescribed antimicrobials were antibiotics (89.9%), the most used was ceftriaxone, metronidazole and ampicillin and these alone accounted for 61.2% of the total antimicrobials prescribed. Injectable formulations of antimicrobials accounted for 34.0% of the total antimicrobials prescribed. The authors discussed that their findings were above WHO prescribing indicators. The WHO standard of percentage of encounters with an antibiotic prescribed is < 30%, but their findings showed 64.5%. These values were noted to be higher than that of Eastern Mediterranean, Americas and European regions. Possible reasons for the higher rate include higher burdens of comorbidities in patients, higher rates of local infections, lack of diagnostics leading to empiric treatment or a shortage of essential medicines forcing prescribers to combine medicines to have intended therapeutic effect. The WHO standard of percentage of encounters with an injection prescribed is < 20%, but 34.0% was observed. The risk of these formulations is the establishment of blood-borne infections. The authors state that their study’s findings suggest overprescribing for non-communicable conditions and that 68.9% of prescriptions for infectious conditions did not include first-line antimicrobial therapy, but instead broad-spectrum antibiotics.

Another study in Nigeria found similar results in their outpatient prescriptions of a tertiary teaching hospital (Okoro et al., 2019). Of 802 prescriptions analysed, antibiotics made up 8.6% of all the prescribed medicines. The average number of antibiotics per patient encounter was 1.3. The most common antibiotic classes prescribed included penicillins (43.3%), nitroimidazoles (22.2%) and fluoroquinolones (20.0%). Amoxicillin/clavulanic acid was the most frequently prescribed in the penicillins (73.1%) and metronidazole in the nitroimidazoles (78.7%). Of the antibiotic prescriptions, 70.5% contained one antibiotic (43.0% were amoxicillin/clavulanic acid), 28.4% contained two antibiotics (33.7% were amoxicillin/clavulanic acid and metronidazole combination) and 1.0% contained three antibiotics. This study did not assess the appropriateness of the antibiotic prescriptions, unfortunately, as it would have provided valuable insights into the decision-making process behind the concurrent use of two antibiotics with overlapping anaerobic coverage.

The following studies examined not only antimicrobial utilisation, but also evaluated their appropriateness or compliance with available guidelines or resources. A study conducted in primary healthcare facilities in Botswana reported that antibiotics prescribed for 87.0% of conditions were compliant with the International Classification of Diseases (ICD) codes, but reasons for non-compliance includes no established diagnosis and mismatch of the ICD code and prescribed antibiotics (Mashalla et al., 2017). This higher adherence to available guidelines was similar to a study conducted in Tanzania, where Kilipamwambu et al. (2021) reported 97.6% adherence to the national essential medicine lists. Another study in Ivory Coast, however, evaluated the antibiotic prescriptions using the reference book of the French-speaking Society of Infectious Pathology and reported that 66.4% of the antibiotic prescription lines were noncompliant according to indication (Eric and Serges, 2019). The authors did note that the antibiotic prescriptions were at least compliant according to route of administration (94.0%) and dosage (70.6%).

Comparing international published literature and findings in South Africa, there are many similarities present. Common prescribing errors highlighted in internationals studies, such as inappropriate antimicrobial selection, dosage, duration and route of administration, have been demonstrated in South African studies. Gasson, Blockman and Willems (2018) highlighted that primary healthcare facilities only had 45.1% of cases of guideline adherence with prevalent overprescribing and prescribing errors. The study conducted by Hlalo (2018) also demonstrated that just over half of amoxicillin/clavulanic acid prescriptions were correctly indicated for the diagnosis. The two studies conducted in the ED of South African hospitals also failed to show promising results (Kudsk-Iversen et al., 2014; Almansoori and Parag, 2021).

The urgent need for an intervention in the use of antimicrobials within the ED is driven by several critical factors. The growing global challenge of AMR, exacerbated by inappropriate antimicrobial prescribing in EDs, may have significant public health implications, including increased mortality, longer hospital stays and higher medical costs (González-del Castillo et al., 2017; Acquisto and May, 2020). Emergency departments face unique challenges, such as diagnostic uncertainty and high-pressure environments, which often lead to non-adherence to antimicrobial guidelines and overreliance on broad-spectrum antibiotics (Bishop, 2016; Yonts et al., 2018; Acquisto and May, 2020). This not only undermines patient safety and care quality, but also contributes to unnecessary healthcare costs (Akenroye et al., 2014; Acquisto and May, 2020). A notable gap exists in adherence to established clinical guidelines for antimicrobial prescribing, possibly due to a lack of awareness or adequate training among healthcare professionals (Bishop, 2016; Acquisto and May, 2020; May et al., 2021). Tailored antibiotic stewardship strategies are needed to address the unique operational dynamics of the ED (Bishop, 2016; Pulia et al., 2018; Acquisto and May, 2020). Interventions are needed to bridge the gap between current practices and optimal antibiotic stewardship, aligning with national and global health initiatives to combat AMR (Ouldali et al., 2017; Yonts et al., 2018). It would also play a crucial role in educating healthcare professionals, enhancing operational efficiency and ensuring long-term sustainability in response to infectious disease challenges (Bishop, 2016). Moreover, a change in antimicrobial prescribing practice would contribute to global health security and public awareness about the importance of appropriate antimicrobial use, underscoring its significance beyond this immediate healthcare setting.

Inappropriate use of antimicrobials, encompassing overprescribing, prescribing errors, and non-adherence to clinical guidelines, has become a pervasive issue in healthcare settings around the world. This practice not only undermines patient care but also contributes significantly to the growing crisis of AMR (Yonts et al., 2018). While there is a general awareness of this issue, the ED represents a unique and critical setting (Bishop, 2016; Acquisto and May, 2020). Despite the crucial role of EDs in the healthcare system, there is a notable paucity of comprehensive studies specifically examining the patterns and appropriateness of antimicrobial use in these departments in South Africa. This gap in research is particularly concerning given the potential of EDs to either contribute to or mitigate the problem of AMR (Bishop, 2016; Yonts et al., 2018). This study, therefore, aims to analyse rigorously the use of antimicrobials in a South African public hospital ED assessing the alignment of prescribing practices with established clinical guidelines. Through a detailed examination of prescribing patterns, decisions made and adherence to guidelines in this ED, this research seeks to identify key areas for improvement in antibiotic stewardship. The findings of this study are expected to provide valuable insights into the current state of antibiotic use in South African EDs and to inform the development of possible targeted strategies to promote appropriate antibiotic use, ultimately contributing to the global effort to combat AMR.

Chapter 3: Research methods

This chapter provides an overview of the research methodology used to conduct the study. It describes the choices of the study design, study site and sample population. It describes the data collection tool used, reliability and validity tests and the study procedure that was carried out. It outlines the ethical considerations considered with necessary permissions obtained. The process followed in analysing the data collected has also been outlined.

3.1 Ethical considerations

An ethics application was submitted to and approved by the WITS-HREC (M210335) (Appendix A). Permission was obtained from the Helen Joseph Hospital Ethics and Research Committee to review patient medical records such as patients' prescriptions and laboratory test results (Appendix B). The protocol was registered on the NDoH Research Database (GP_202105_059). No patients' permissions were needed to access information from their medical records, as this was a retrospective review. All the information that was collected in the study from the patient medical records was kept confidential by omitting names and other identifiable information of participants, such as identification numbers. This is in accordance with the Protection of Personal Information Act. Data collected has been stored on an online drive with its access limited to the researcher and supervisors through password protection using Research Electronic Data Capture (REDCap) software. The study commenced once ethics approval was obtained.

3.2 Study design

A quantitative, retrospective cross-sectional study design was selected for the review of patient medical records from the ED of Helen Joseph Hospital in Johannesburg, Gauteng. These patient medical records were reviewed for appropriateness and correctness of the antimicrobials prescribed in accordance with South African STG, SAASP and the SAMF.

A quantitative study was chosen as this study is a drug utilisation review that looks at trends in prescribing of antimicrobials to determine practices that may be contributing to AMR. The main category applied was that of a descriptive (observational) design. The descriptive measures included the prevalence of appropriateness or inappropriateness of prescriptions and the analytical measures assisted in identifying any associations between the different parameters, allowing for the study of associations of possible predictors of inappropriate antimicrobial prescribing (Kesmodel, 2018; Wang and Cheng, 2020). A retrospective study was chosen as existing medical records were used which allowed for the observation of a larger population over a year, and allowed for the analysis of antimicrobial prescribing patterns from routine emergency medical care in the South Africa public sector (Hess, 2004; Abbott et al., 2016).

3.3 Study site

The study was conducted in the records department of Helen Joseph Hospital located in Auckland Park, Johannesburg. Archived patient medical records originating from the ED were accessed. The study site is a 700 - bed tertiary public hospital, providing practical training for healthcare students and is a facility for research for students from the University of the Witwatersrand. The institution receives referrals from many other public institutions in Gauteng, such as primary healthcare clinics and district hospitals, providing an optimal site for data collection, representative of a large enough population.

3.4 Population and sample

3.4.1 Study participants and sample size

The ED at Helen Joseph Hospital consulted with approximately 52 822 patients during the period of 01 August 2020 to 31 July 2021. This institution's ED cares for a wide variety of patients with varying demographics, providing a broad population group for this study. The hospital lies between residential areas and is in close proximity to low-income areas. In low-income settings there are factors that may exacerbate infections, such as poor nutrition, unsanitary living conditions, unemployment and lack of health education. The sample size was calculated using Raosoft software with 850 patient medical records in total needed for this study (Raosoft, 2004). The equation below was used on the Raosoft software. A prevalence of 10% of total prescriptions for antimicrobial therapy was accepted as per a previous study (Timbrook et al., 2017). A precision rate of ±2.00% (one-fifth of prevalence) and 95% confidence interval was selected to calculate sample size (Pourhoseingholi et al., 2013). Each prescription was randomly selected until the saturation of 850 patient medical records was reached.

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

n = sample size as a percentage of total population

Z = statistic corresponding to level of confidence (Confidence Interval of 95%)

P = expected prevalence

d^2 = precision (one-fifth of prevalence)

Equation 1: Sample size equation

3.4.2 Inclusion criteria

Patients' medical records reviewed were those who had received a prescription with an antimicrobial agent while in and upon discharge from the ED. All conditions and diagnoses listed were included, unless they were disregarded as per the exclusion criteria. Patients of all ages were included in this study. These patient medical records were included as they offered a wide range of ages, each with their own challenges for the prescribing of antimicrobial agents. As these patients were sent home with the antimicrobial agent and instructions on the dosage regimen, there was a second review concerning appropriateness from other healthcare workers.

3.4.3 Exclusion criteria

Patients' medical records were excluded if they were admitted to the hospital following the ED or if antimicrobials were given for pre or postoperative prophylaxis. Furthermore, exclusion was applied to incomplete chart documentation and illegible handwritten prescriptions which resulted in incomprehensive data. Patients' medical records were excluded if the patient received medication for TB and HIV, as these patients would receive the medication from a primary healthcare clinic and not the study site.

3.4.4 Sampling method

A random sampling method was used. This is considered the gold standard for retrospective patient medical record review studies. Triage books for each month were accessed and patients' medical records were chosen at random and included if they met the criteria until target number were met. This sampling method ensured patient medical records from the chosen population are selected at random, ensuring each opportunity for analysis. Random selection helped to generalise the results of the population and eliminated sampling bias (Vassar and Holzmann, 2013).

3.5 Study procedure

3.5.1 Data collection tool

Data collected was assessed for appropriateness by using the MAI (Hanlon et al., 1992), which is a free validated tool used to determine prescribed medicine appropriateness and has been used successfully in previous studies (Hanlon and Schmader, 2013). The MAI consists of standardised questions which assess appropriateness of the prescription by looking at ten different areas of medication prescribing, such as indication, effectiveness, dosage, directions, practicality, drug-drug interactions, duplication, duration and cost of the medication as listed in Appendix F (Hanlon et al., 1992; Timbrook et al., 2017). This tool was modified in accordance with requirements for this study, and to allow for the evaluation of the antimicrobial prescribed with its indication, dose, duration, route, frequency and microbial suppressibility; aligned to the STG for hospital level for adults and paediatrics, SAASP and SAMF and pathogen susceptibility results, when available. In the final question of the tool, the prescriptions are deemed either appropriate or inappropriate after analysis (Timbrook et al., 2017). The MAI tool was the foundation for data analysis, captured on REDCap software and transcribed for analysis on Microsoft Excel (Hanlon et al., 1992, Timbrook et al., 2017). REDCap is web-based software available for designing and managing databases and surveys online (Harris et al., 2009, 2019).

3.5.2 Reliability and validity of data collection tool

The reliability and validity of the MAI tool has been reviewed in previous studies and has been concluded to be an effective tool for measuring inappropriate prescribing (Hanlon and Schmader, 2013; Awad and Hanna, 2019; Müller et al., 2020). The MAI has been shown to have acceptable inter- and intra-rater reliability, as it detects more potentially inappropriate prescribing than other used sets of explicit criteria, and has a good prediction of adverse health outcomes indicating the impact of interventions to address the identified public health problem (Hanlon and Schmader, 2013, 2022).

A pilot study was conducted in order to acquire the reliability and validity of the modified tool. The pilot study was a small-scale study aimed at assessing if the adaptations made to consider the South African healthcare context, allowed for the necessary data to be obtained for analysis (Thabane et al., 2010). The pilot study's sample size was 19 patient medical records, which was more than the recommended 10% of the sample size calculated for each month (which was a minimum of 71 patient medical records) (Connelly, 2008). The patient medical records included in the pilot study were excluded in the parent study.

Amendments made to the original MAI are tabulated with detailing the reasoning for these adaptions (Appendix F). Results of culture specimens were also documented, which helped to assess the appropriateness regarding the microorganism's susceptibility and to compare the results to the antimicrobial choice in the guidelines. Co-morbidities were included in the demographic data because many antimicrobial choices in the guidelines are influenced by this, such as CAP, UTIs and acute inflammatory diarrhoea (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b, 2020).

Inter-rater reliability testing was completed by the supervisors in this study. The study supervisors re-abstracted a sample of the prescriptions, blinded to the information and evaluation obtained by the principal researcher (Gilbert et al., 1996). In order to carry out inter-rater reliability, a minimum of two abstractors were needed, as it presents in this study, as there is a principal researcher and two supervisors (Allison et al., 2000). If the principal researcher and supervisors have the identical interpretations of the data abstracted from the prescriptions on the data collection sheet, the accuracy and consistency in the assessment was confirmed. A representative sample, of 85 patient medical records, from the total sample size was used for inter-rater reliability testing. The data collection tool was validated by conducting a pilot study on 19 patient medical records before the commencement of the parent study to further ensure that it was reliable and valid tool in the South African healthcare and parent study's context (Temel and Erdogan, 2017).

3.5.3 Review of Patient Medical Records

Patient medical records were accessed from the archives room, manually retrieved and reviewed on site. The number of patient medical records reviewed and included in the study was a total of 850, for the period of 01 August 2020 to 31 July 2021. The researcher accessed, screened, selected and reviewed eligible prescriptions that met inclusion criteria, during the stated study period. Patient medical records opened by the ED during each month in this period, that were randomly chosen from triage record books, were screened for antimicrobials prescribed, diagnoses and/or the ICD codes written. The patient medical records that had antimicrobials prescribed, microbial infection diagnoses, ICD codes indicating microbial infection diagnoses or diagnoses that required antimicrobial treatment were included in the study for review. The sample size was divided over 12 months. The patient medical records of each month were screened until a minimum of 71 patient medical records were reached for that month. Data extracted included: age, sex, diagnosis of infection, antimicrobial prescribed (dose, route, frequency, duration, strength), any chronic medications, any co-morbid conditions, presence and sensitivity of the microorganism to certain antimicrobials as per the National Health Laboratory Service guidelines, medicine allergies, temperature, serum creatinine, C-reactive protein (CRP), white blood cell count (WCC) and procalcitonin (PCT) levels, height and weight. Signs and symptoms, ICD codes and reappearance in the ED with the same signs and symptoms within 14 days of last consultation at the ED were also noted, if available. Through analysis of ICD codes or diagnoses documented by the prescriber, it was determined if an antimicrobial should have been prescribed but may have been omitted. Appropriateness was determined if the correct antimicrobial was chosen for the correct indication, with the correct route of administration and if the correct dose at the correct frequency was prescribed for the correct duration of time. If culture susceptibility results were available, the researcher assessed whether the antimicrobial supplied was appropriate according to guidelines. Any drug interactions, antimicrobial allergies and contra-indications were documented as per the prescribers' notes. The data collected from the reviewed patient medical records were then compared to recommended treatments in published guidelines, such as in the Department of Health Hospital STGs for hospital level for adults and paediatrics guidelines, EDL, SAASP and SAMF. The decision of adherence to guidelines and appropriateness were only based on the most recent published guidelines available and accessible at the time of the study period. Cost efficiency was assessed by comparing the cost of the antimicrobial/s prescribed to the antimicrobial therapy suggested by the guidelines, considering the duration, frequency, strength and route of administration. The relevant Monthly Index of Medical Specialities for the study period was used to assess the cost-effectiveness of the chosen antimicrobial therapies. This is only an estimation because the exact brand of each of the antimicrobials could not be confirmed as medicines in the public healthcare sector can be supplied based on tenders and availabilities, and medicines are often prescribed as active ingredients and not trade names. The principal researcher and supervisors all had previous working experience in public healthcare pharmacies and, when calculating cost, would choose the trade name that was most commonly encountered in these settings. The chosen trade name of the antimicrobial was used throughout the study when comparing costs.

3.6 Data analysis

Data analysis was completed using Microsoft Excel and Statistica software version 14 (TIBCO Software Inc., 2020). Descriptive statistics were used to reflect patient characteristics, (demographics), clinical diagnosis and characteristics of the prescribed antimicrobial. Bivariate analysis using Pearson's chi-square test and Fischer's exact test was used for categorical data, such as sex, diagnosis and antimicrobial category and class (Alanazi et al., 2015). Continuous variables, such as age, temperature and CRP values, were either presented as means and standard deviations if normally distributed or median and interquartile ranges where data was not normally distributed. Prevalence was measured using frequency and percentages. Significance is considered at a p-value <0.05 (Alanazi et al., 2015). Kappa statistics for inter-rater reliability was calculated for the overall MAI and MAI categories per STG, EDL and SAASP guidelines based on Timbrook et al, (2017) study. A value of Kappa below 0.60 indicates inadequate agreement between the raters and a value above 0.60 indicates adequate agreement, with 0.80 to 0.90 indicating strong agreement and values above 0.90 indicating almost perfect agreement (McHugh, 2012).

Chapter 4: Results and discussion

This chapter presents the findings of the retrospective analysis and interpretation of patient medical records and prescriptions that were collected from the ED of Helen Joseph Hospital. This chapter depicts and reviews the antimicrobial prescribing patterns and appropriateness of physicians positioned in this hospital department and highlights the most common antimicrobials prescribed. This chapter begins with a brief description of the pilot study. Following this, it describes the results for each objective and provides a comprehensive discussion of these results with reference to published literature.

4.1 Pilot Study

A pilot study was conducted in which 19 patient medical records were examined to determine the capacity of the modified MAI to be used in this study to provide suitable results in relation to the study objectives. The calculated sample size accounts for over ten percent of one month's expected prescription records collected (Hertzog, 2008). Data was collected from these patient medical records and was shared with the study supervisors to determine if the information was sufficient and accurately interpreted. The inter-rater reliability study indicated that the modified tool was compatible for South African data and reliable for analysis; therefore, the study was continued. A Kappa value of 0.80 was calculated which indicates a strong agreement between the original MAI tool and the MAI tool modified for this study (McHugh, 2012). Kappa statistics could not be calculated between raters due to the lack of negative agreement.

4.2 Objective 1: Antimicrobial prescribing patterns of physicians in the ED

4.2.1 Patient demographics

Table 2 represents the results obtained concerning patient demographics. The table also summarises the relationship between these results and whether an antimicrobial was prescribed. Of the 850 patient medical records reviewed, most patients were male (54.4%, n=462) and comprised 55.0% (n=431) of antimicrobial prescriptions. The mean age (±standard deviation) was 38.5 ± 15.6 years, with patients between the ages of 36 to 64 years old being the most common (44.1%, n=375). Patients between the ages of 65 to 100 years received the highest number of antimicrobial prescriptions per patient (95.3%, n=61/64). Co-morbidities were recorded in 38.7% (n=329) of patients, with the most recorded co-morbidity being HIV/AIDS followed by hypertension and type two diabetes mellitus. Patients with or without co-morbidities both had similar percentages of antimicrobial prescriptions. Only 282 patients (33.2%) reported being on chronic medications and showed no significant difference in receiving antimicrobial prescriptions. Nineteen patients (2.2%) revisited the ED within 14 days with the same complaint. A study conducted in Spain that assessed the inadequacy of antibiotic therapy in the ED found that 19.7% of patients were re-admitted to the facility within 30 days of the index event. This value is a lot higher compared to this study's findings, but this may be attributed to the higher time period of 30 days (González-del Castillo et al., 2017). Of the 19 patients that revisited the ED, 10 patients (52.6%) were admitted into hospital.

Table 2: Patient characteristics and frequency of antimicrobial prescriptions.

Characteristics	**Total n (%) (n=850)**	**Antimicrobials prescribed, n (%) (n=784)**	**Antimicrobials not prescribed, n (%) (n=66)**	***p*-value**
Sex				
Male	462 (54.4)	431 (55.0)	31 (47.0)	
Female	388 (45.6)	353 (45.0)	35 (53.0)	0.21
Age				
Mean ± SD	38.5 ± 15.6	38.6 ± 15.7	37.3 ± 14.9	
0-17 years	40 (4.7)	34 (4.3)	6 (9.1)	
18-35 years	371 (43.6)	346 (44.1)	25 (37.9)	
36-64 years	375 (44.1)	343 (43.8)	32 (48.5)	
65-100 years	64 (7.5)	61 (7.8)	3 (4.5)	0.241
Co-morbidities				
Yes	329 (38.7)	304 (38.8)	25 (37.9)	
HIV/AIDS	142 (43.2)	127 (41.8)	15 (60.0)	
Hypertension	117 (35.6)	107 (35.2)	10 (40.0)	
Other	89 (27.1)	84 (27.6)	5 (20.0)	
Type II Diabetes Mellitus	60 (18.2)	56 (18.4)	4 (16.0)	
Asthma	23 (7.0)	23 (7.6)		
High Cholesterol	18 (5.5)	17 (5.6)	1 (4.0)	
COPD	10 (3.0)	9 (3.0)	1 (4.0)	

Table 2: Patient characteristics and frequency of antimicrobial prescriptions continued.

Characteristics	Total n (%) (n=850)	Antimicrobials prescribed, n (%) (n=784)	Antimicrobials not prescribed, n (%) (n=66)	*p*-value
Epilepsy	8 (2.4)	8 (2.6)		
No	500 (58.8)	461 (58.8)	39 (59.1)	
Not recorded	21 (2.5)	19 (2.4)	2 (3.0)	0.949
Chronic medicines				
Yes	282 (33.2)	256 (32.7)	26 (39.4)	
No	518 (60.9)	480 (61.2)	38 (57.6)	
Not recorded	50 (5.9)	48 (6.1)	2 (3.0)	0.376
Drug allergies				
Yes	17 (2.0)	13 (1.7)	4 (6.1)	
Penicillin	11 (64.7)	8 (61.5)	3 (75.0)	
Iodine	1 (5.9)	1 (7.7)		
Other	5 (29.4)	4 (30.8)	1 (25.0)	0.721
No	717 (84.4)	662 (84.4)	55 (83.3)	
Not recorded	116 (13.6)	109 (13.9)	7 (10.6)	**0.04**
Temperature (°C)				
Mean ± SD	35.1 ± 7.1	35.0 ±7 .3	35.9 ± 4.5	
30.0-35.9	49 (5.8)	45 (5.7)	4 (6.1)	
36.0-37.9	739 (86.9)	680 (86.7)	59 (89.4)	
38.0-41.0	29 (3.4)	27 (3.4)	2 (3.0)	
Not recorded	33 (3.9)	32 (4.1)	1 (1.5)	0.702
CRP (mg/L)				
Mean ± SD	63.8 ± 79.7	64.1 ± 80.3	29.7 ± 0.6	
≤4	28 (3.3)	28 (3.6)		
>4	115 (13.5)	112 (14.3)	3 (4.5)	
Not measured	707 (83.2)	644 (82.1)	63 (95.5)	**0.019**

Table 2: Patient characteristics and frequency of antimicrobial prescriptions continued.

Characteristics	Total n (%) (n=850)	Antimicrobials prescribed, n (%) (n=784)	Antimicrobials not prescribed, n (%) (n=66)	*p*-value
WCC (x10^9/L)				
Mean ± SD	9.5 ± 4.7	9.6 ± 4.7	8.9 ± 6.1	
<4.0	6 (0.7)	6 (0.8)		
4.0-10.8	81 (9.5)	79 (10.1)	2 (3.0)	
>10.8	43 (5.1)	42 (5.4)	1 (1.5)	
Not measured	720 (84.7)	657 (83.8)	63 (95.5)	**0.036**
Specimens sent for microscopy, culture and susceptibility testing				
Yes	41 (4.8)	41 (5.2)		
No	809 (95.2)	743 (94.8)	66 (100.0)	0.067
Revisit to the ED within 14 days with the same complaint				
Yes	19 (2.2)	16 (2.0)	3 (4.5)	
No	831 (97.8)	768 (98.0)	63 (95.5)	0.178
Number of diagnoses				
One	837 (98.5)	771 (98.3)	66 (100.0)	
Two	10 (1.2)	10 (1.3)		
Three	3 (0.4)	3 (0.4)		0.347

Abbreviations: COPD: chronic obstructive pulmonary disorder; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; SD: standard deviation; WCC: white cell count.

Note: Significance is displayed in bold; percentages may not equal 100% due to rounding to one decimal place; patients could have more than one co-morbidity

Only 86.4% (n=734) of medical records documented whether the patient had a possible drug allergy. In the cases where allergies were not recorded (13.6%, n=116), antimicrobials were still prescribed in 93.1% (n=108) of these cases, as displayed in Table 3. The lack of documenting the patient's allergy status is considered a risky approach to prescribe any medication, especially as antimicrobials have a higher tendency to induce a drug allergy and the recording of an allergy is used to prevent medical errors (Khalil et al., 2011; Alanazi et al., 2015).This is concerning, because antibiotics, especially penicillin, are the most reported group of medications to cause allergies, with self-reported cases amongst roughly five to ten percent of patients (Macy and Poon, 2009; Gay et al., 2010; Moskow et al., 2016). This value, however, may be lower as 85% to 90% of these patients have shown negative skin tests to penicillin (Riedl and Casillas, 2003; Solensky, 2004; Moskow et al., 2016). Comparing these values to this study's findings, only 1.3% of patients reported having a penicillin allergy. There was one patient is this study that received a penicillin antibiotic, with a blank allergy record in the medical chart and returned the following day to the outpatient department to report an allergic reaction and sought treatment. This may have been prevented if the allergy was correctly recorded (if the allergy was already known to the patient). A point prevalence survey of penicillin allergies in hospitalised patients in Cape Town demonstrated that 3.2% patients had a self-reported penicillin allergy, but only 52.1% of these patients had this documented in their patient notes or prescription charts and 22 patients received a beta-lactam-containing antibiotic in hospital without prior screening (Day et al., 2022). This study did indicate the lower burden of self-reported penicillin allergy in Cape Town and may suggest the allergy rates are lower in this African population, but still observed the poor recording of these allergies and the risk for medication errors (Day et al., 2022). The number of allergy recordings was interestingly higher compared to Alanazi et al. (2015) study in Saudi Arabia, where only 7.9% of cases documented the patients' allergy status and this is commendable on South Africa's allergy documenting practice, but still needs to be further enforced for patient safety.

Table 3: Number and type of antimicrobials prescribed when no allergy was stated or recorded.

Antimicrobials prescribed with no allergy recorded, n (%)	
Yes	108 (93.1)
No	8 (6.9)
Type of antimicrobials prescribed, n (%)	**Total n=109**
Antibacterial	107 (99.1)
Penicillins	89 (83.2)
Macrolides	14 (13.1)
Fluoroquinolones	7 (6.5)
Nitroimidazoles	6 (5.6)
Cephalosporins	5 (4.7)
Tetracyclines	4 (3.7)
Amphenicols	2 (1.9)
Lincosamides	1 (0.9)
Phosphonic acid derivative	1 (0.9)
Antiviral	1 (0.9)
Nucleoside and nucleotide analogues	1 (0.9)
Antifungal	1 (0.9)
Triazole derivatives	1 (0.9)

Note: Patients could receive more than one type of antimicrobial and class of antimicrobial in a single prescription

4.2.2 Clinical features and diagnostic test results

Temperature readings were a regularly tested parameter in the ED. The mean temperature of patients reviewed was 35.0°C ± 7.0°C (± SD), with majority of temperature readings being within normal ranges of 36.0°C to 37.9°C (86.9%, n=739) as displayed in Table 2. Antimicrobial prescriptions were mostly prescribed in patients within the normal temperature range (86.7%, n=680), however, proportionally there was an increase in antimicrobial prescriptions in the rise of temperature. Ninety-seven percent of patients who did not have a recorded temperature received antimicrobials.

Additional diagnostic measurements, that are not routine, included CRP and WCC results. The CRP was tested in 16.8% (n=143) of cases and WCC tested in 15.3% (n=130) of cases. The majority of CRP test results were above 4 mg/L (80.4%, n=115) and only 19.6% (n=28) were within the standard range of ≤ 4 mg/L. Most of the WCC results were within standard ranges of 4.0 to 10.8 x 10^9/L (62.3%, n=81) with only six (4.6%) cases below normal ranges and 43 (33.1%) cases above. To note, the patients with the standard values of CRP all received antibiotics and 97.5% (n=79/81) patients with WCC within standard range received antibiotics. The limitation of CRP and WCC use in the ED is that they lack specificity and reliability in diagnosis and treatment decisions, as CRP is a general marker of inflammation and WCC is influenced by various factors, leading physicians not to rely solely on these tests (Seigel et al., 2012; Su, 2014; Eric and Serges, 2019).

Only 41 patients had specimens sent for microscopy, microbial culturing and antimicrobial susceptibility testing. This was only 5.2% of the patients who were prescribed antimicrobials. Urine specimens were most common (64.3%), followed by pus aspirates (23.8%) (Table 4). Only 50% of the specimens sent for microbiological analysis had positive microorganism growth (20 bacterial cultures and one fungal culture). Ideally, culture results would allow for ED culture follow up and adjustment in antimicrobial therapy based on the causative pathogen (Almulhim et al., 2019; May et al., 2021; Sapozhnikov et al., 2024). This may prove to be difficult in the South African public ED setting, due to the delay in receiving culture results and patients recovering from initial aliments because of broad-spectrum antibiotic usage. Time constraints, lack of infrastructure and limited human resources hinder this practice (Acquisto and May, 2020; May et al., 2021). Many studies, however, have assessed the effectiveness of pharmacists in the role of ED culture follow ups with positive findings (Santiago et al., 2016; Dumkow et al., 2017; Zhang et al., 2017; Dumkow et al., 2018; Almulhim et al., 2019; Fay et al., 2019; Giruzzi et al., 2020). The benefit of sending specimens for culture and susceptibility testing would help collect valuable data to create antibiograms for the ED to guide future antimicrobial prescriptions (May et al., 2013; Pulia et al., 2018; Acquisto and May, 2020; May et al., 2021).

Table 4: Types of specimens sent for microscopy, culture and susceptibility testing and results.

Types of specimens	Total, n (%) n=42*	Positive culture n= 21	Microorganisms cultured	Negative culture n= 21
Urine	27 (64.3)	12 (57.1)	*Escherichia coli*, *Proteus mirabilis*	15 (71.4)
Pus aspirate#	10 (23.8)	6 (28.5)	*Staphylococcus aureus*, *Staphylococcus hominis, Streptococcus pyogenes*	4 (19.1)
Stool	2 (4.7)			2 (9.5)
Blood	1 (2.4)	1 (4.8)	*Bacillus species*	
Ear swab	1 (2.4)	1 (4.8)	*Staphylococcus capitis*	
Sputum	1 (2.4)	1 (4.8)	*Candida albicans*	

*One patient had two specimens sent for microscopy, microbiological culturing and susceptibility testing

#Pus aspirates were all taken from suspected diagnoses of abscesses; one specimen grew two microorganisms

4.2.3 Diagnoses

In the 850 patient medical records reviewed, a total of 866 diagnoses were recorded. The majority of patients had one diagnosis (98.5%, n=837) and the remainder had either two or three diagnoses, as displayed in Table 2. Table 5 summarises the diagnoses and details whether antimicrobials were prescribed for each. Condition categories that were commonly diagnosed and prescribed antimicrobials were skin and soft tissue conditions, followed by trauma and injuries, lower respiratory tract conditions, urinary tract conditions and reproductive system conditions. All urinary tract conditions, dental and oral conditions, cardiovascular conditions and central nervous system conditions received antimicrobials. The leading diagnoses resulting in an antimicrobial prescription were UTIs (11.5%, n=92) followed by CAP (8.0%, n=64), abscesses (7.1%, n=57), soft tissue injuries (6.1%, n=49) and cellulitis (5.3%, n=42). Patients presenting with urinary tract complaints were more likely to receive antimicrobials ($p=0.001$, $p <0.05$), especially those with community-acquired UTIs ($p=0.003$, $p<0.05$). Patients presenting with trauma and injuries, specifically those with animal bites were less likely to receive antimicrobials ($p<0.0001$, $p <0.05$), whereas those diagnosed with soft tissue injuries were more likely to result in antimicrobial prescriptions ($p=0.03$, $p<0.05$). Patients diagnosed with lower respiratory tract conditions were more likely to receive antimicrobials compared to those not diagnosed ($p=0.02$, $p<0.05$).

Reflecting on these detailed patterns of antimicrobial use, it becomes evident that studies in different regions provide a broader context, revealing diverse priorities and challenges in managing infections. A study that examined antimicrobial prescribing patterns in a large tertiary hospital's outpatient and ED in Shanghai, reported that diseases of the respiratory system received over 40% of the total antimicrobials prescribed (Wang et al., 2016). This was then followed by diseases of the digestive system and genitourinary system. The authors also noted that 7% of antimicrobial prescriptions did not have clear indications for bacterial infections in diagnoses such as injuries or diseases of the circulatory system (Wang et al., 2016). Yi et al. (2022) in Liberia, found that abdominal infections received the most antimicrobial prescriptions, followed by malaria and UTIs. In a similar study in South Africa, Almansoori and Parag (2021) reported that abscesses obtained the antimicrobial prescriptions followed by "sepsis/infection", appendicitis and cellulitis. The contrast between these studies highlights the diversity in medical conditions leading to antimicrobial prescriptions, underlining significant regional variations in healthcare practices based on the local burden of disease and healthcare priorities.

Table 5: Diagnoses with and without prescribed antimicrobials.

Diagnosis	**Total, n (%)** **n=866**	**Antimicrobials prescriber per diagnosis, n (%)** **n=800**	**Antimicrobials not prescribed per diagnosis, n (%)** **n=66**	***p*-value**
Skin and soft tissue conditions	**171 (19.8)**	**157 (19.6)**	**14 (21.1)**	0.82
Abscess	58 (33.9)	57 (36.3)	1 (7.1)	0.08
Cellulitis	44 (25.7)	42 (26.8)	2 (14.3)	0.57
Complicated leg ulcers	16 (9.4)	9 (5.7)	7 (50.0)	**<0.0001**
Other*	14 (8.2)	14 (8.9)		0.62
Diabetic foot ulcers	11 (6.4)	9 (5.7)	2 (14.3)	0.21
Shingles	10 (5.8)	10 (6.4)		1.00
Surgical wound infections	5 (2.9)	5 (3.2)		1.00
Paronychia	5 (2.9)	5 (3.2)		1.00
Pressure sores	3 (1.8)	2 (1.3)	1 (7.1)	0.22
Chickenpox	2 (1.2)	1 (0.6)	1 (7.1)	0.15
Acne vulgaris	1 (0.6)	1 (0.6)		1.00

Table 5: Diagnoses with and without prescribed antimicrobials continued.

Diagnosis	Total, n (%) n=866	Antimicrobials prescriber per diagnosis, n (%) n=800	Antimicrobials not prescribed per diagnosis, n (%) n=66	*p*-value
Impetigo	1 (0.6)	1 (0.6)		1.00
Scabies	1 (0.6)	1 (0.6)		1.00
Trauma and injuries	**166 (19.2)**	**129 (16.1)**	**37 (56.1)**	**<0.0001**
Animal bites	71 (42.8)	38 (29.5)	33 (89.2)	**<0.0001**
Soft tissue injuries	49 (29.5)	49 (38.0)		**0.03**
Human bites	28 (16.9)	24 (18.6)	4 (10.8)	0.27
Head injuries	14 (8.4)	14 (10.9)		0.62
Burns	4 (2.4)	4 (3.1)		1.00
Lower respiratory tract conditions	**136 (15.7)**	**132 (16.5)**	**4 (6.1)**	**0.02**
CAP	66 (48.5)	64 (48.5)	2 (50.0)	0.14
COVID-19	27 (19.9)	27 (20.5)		0.23
Other*	27 (19.9)	27 (20.5)		0.23
Asthma	7 (5.1)	7 (5.3)		1.00
AECOPD	7 (5.1)	5 (3.8)	2 (50.0)	0.08
Bronchitis	2 (1.5)	2 (1.5)		1.00
Urinary tract conditions	**106 (12.2)**	**106 (13.3)**		**0.001**
UTI	92 (86.8)	92 (86.8)		**0.003**
Catheter associated UTI	8 (7.5)	8 (7.5)		1.00
Other*	3 (2.8)	3 (2.8)		1.00
Renal calculi	3 (2.8)	3 (2.8)		1.00
Reproductive system conditions	**97 (11.2)**	**93 (11.6)**	**4 (6.1)**	0.16
Scrotal swelling	28 (31.5)	28 (30.1)		0.16
MUS	17 (19.1)	17 (18.3)		0.64
Paraphimosis	11 (12.4)	10 (10.8)	1 (25.0)	0.60
PID	8 (9.0)	8 (8.6)		1.00
Anogenital warts	6 (6.7)	3 (3.2)	3 (75.0)	**0.008**
Other*	6 (6.7)	6 (6.5)		1.00
GUS	5 (5.6)	5 (5.4)		1.00
STI prophylaxis	4 (4.5)	4 (4.3)		1.00

Table 5: Diagnoses with and without prescribed antimicrobials continued.

Diagnosis	Total, n (%) n=866	Antimicrobials prescriber per diagnosis, n (%) n=800	Antimicrobials not prescribed per diagnosis, n (%) n=66	*p*-value
Syphilis	3 (3.4)	3 (3.2)		1.00
Vaginal candidiasis	3 (3.4)	3 (3.2)		1.00
Balanitis	2 (2.2)	2 (2.2)		1.00
Bubo	2 (2.2)	2 (2.2)		1.00
VDS	2 (2.2)	2 (2.2)		1.00
Ear, nose and throat conditions	**73 (8.4)**	**71 (8.9)**	**2 (3.0)**	0.09
Tonsillitis	28 (39.4)	28 (39.4)		0.16
Other*	16 (22.5)	16 (22.5)		0.63
Otitis media	14 (19.7)	14 (19.7)		0.62
Sinusitis	6 (8.5)	4 (5.6)	2 (100.0)	0.07
Pharyngitis	5 (7.0)	5 (7.0)		1.00
Peritonsillar abscess	3 (4.2)	3 (4.2)		1.00
Otitis externa	1 (1.4)	1 (1.4)		1.00
Gastro-intestinal conditions	**51 (5.9)**	**49 (6.1)**	**2 (3.0)**	0.42
Acute gastroenteritis	11 (21.6)	11 (22.5)		1.00
Peri-anal abscess	11 (21.6)	10 (20.4)	1 (50.0)	0.59
Other*	7 (13.7)	7 (14.3)		1.00
Acute inflammatory diarrhoea	6 (11.8)	6 (12.2)		1.00
Appendicitis	4 (7.8)	3 (6.1)	1 (50.0)	0.28
Peptic ulcer disease	4 (7.8)	4 (8.2)		1.00
Haemorrhoids	3 (5.9)	3 (6.1)		1.00
Cholecystitis	2 (3.9)	2 (4.1)		1.00
Gastritis	1 (2.0)	1 (2.0)		1.00
Acute non-inflammatory diarrhoea	1 (2.0)	1 (2.0)		1.00
Helminths	1 (2.0)	1 (2.0)		1.00

Table 5: Diagnoses with and without prescribed antimicrobials continued.

Diagnosis	Total, n (%) n=866	Antimicrobials prescriber per diagnosis, n (%) n=800	Antimicrobials not prescribed per diagnosis, n (%) n=66	*p*-value
Ophthalmic conditions	**33 (3.8)**	**32 (4.0)**	**1 (1.5)**	0.51
Herpes Zoster Ophthalmicus	12 (36.4)	11 (34.4)	1 (100.0)	1.00
Foreign bodies	9 (27.3)	9 (28.1)		1.00
Conjunctivitis	7 (21.2)	7 (21.9)		1.00
Other*	4 (12.1)	4 (12.5)		1.00
Keratitis	1 (3.0)	1 (3.1)		1.00
Dental and oral conditions	**16 (1.9)**	**16 (2.0)**		0.63
Dental abscess	7 (43.8)	7 (43.8)		1.00
Oral candidiasis	4 (25.0)	4 (25.0)		1.00
Other*	3 (18.8)	3 (18.8)		1.00
Sialadenitis	2 (12.5)	2 (12.5)		1.00
Musculoskeletal conditions	**6 (0.7)**	**5 (0.6)**	**1 (1.5)**	0.39
Osteomyelitis	3 (50.0)	2 (40.0)	1 (100.0)	0.22
Septic arthritis	2 (33.3)	2 (40.0)		1.00
Other*	1 (16.7)	1 (20.0)		1.00
Other condition groups	**7 (0.8)**	**6 (0.8)**	**1 (1.5)**	0.43
Cardiovascular system	**2 (0.2)**	**2 (0.3)**		1.00
Central nervous system	**2 (0.2)**	**2 (0.3)**		1.00

Abbreviations: AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; GUS: genital ulcer syndrome; LRTI: lower respiratory tract infection; MUS: male urethritis syndrome; PID: pelvic inflammatory disease; STI: sexually transmitted infection; URTI: upper respiratory tract infection; UTI: urinary tract infection; VDS: vaginal discharge syndrome

Note: Not all percentages equal to 100% due to rounding to one decimal place, $p<0.05$ is in bold

*These are diagnoses that were not listed in guidelines or were symptoms listed as diagnoses

4.2.4 Class and Type of Antimicrobials

Antimicrobials were prescribed in 92.2% (n=784) of the patient medical records reviewed. Over half of these patient records had one antimicrobial prescribed (57.7%, n=452), with the remainder receiving two or more antimicrobials (42.3%, n= 332) (Figure 3).

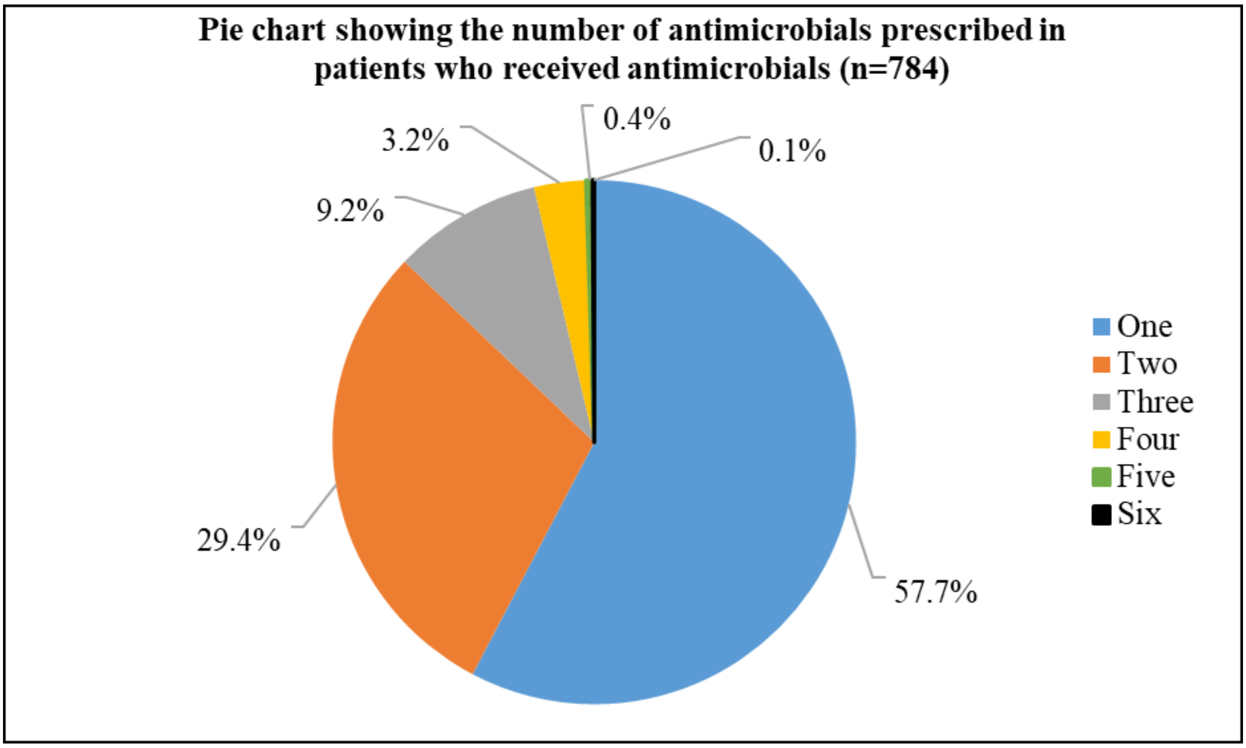

Figure 3: Pie chart displaying the number of antimicrobials prescribed per patient who received antimicrobial prescriptions as a percentage.

The percentage of patients receiving one antimicrobial was lower than Almansoori and Parag's (2021) study within a public hospital's ED in KwaZulu-Natal, where 80.5% of patients received one antimicrobial. This may be suggestive of an overuse of antimicrobials, but there is a study duration difference (over one year compared to one month). A total of 1251 antimicrobials were prescribed (this excludes the actual number of units the patient received for the treatment duration); therefore, the average of antimicrobials prescribed per patient with an antimicrobial prescription was 1.6.

Table 6 displays the different antimicrobials prescribed. The most commonly prescribed group of antimicrobials were antibacterials (96.7%, n=1210), followed by antivirals (2.1%, n=26), antimycotics (1.0%, n=13), antihelmintics (0.1%, n=1) and ectoparasiticides (0.1%, n=1). The six most common prescribed classes of antibacterials were penicillin (63.4%, n=767), macrolides (11.1%, n=134), cephalosporins (7.3%, n=88), nitroimidazole derivatives (7.0%, n=85), fluoroquinolones (4.7%, n=57) and amphenicols (4.1%, n=50). Amoxicillin/clavulanic acid made up 89.2% (n=684) of the penicillin and ceftriaxone made up 87.5% (n=77) of cephalosporins. All macrolides prescribed were azithromycin. The only prescribed class of antivirals was a nucleoside and nucleotide analogue, aciclovir. Only three classes of antimycotics were prescribed and these were imidazole derivatives (clotrimazole and ketoconazole), triazole derivatives (fluconazole) and polyene antifungals (nystatin). This is attributed to the South African EDL that recommends limited antimycotics and antiviral classes, especially for outpatients.

The use of broad-spectrum antibiotics as first-line antibiotic therapy in the ED is expected because of diagnostic uncertainty, limited available patient information, need for quick decision making and risks of patients' health in antibacterial administration delays (Trinh and Klinker, 2015; Bishop, 2016; May et al., 2021). These broad-spectrum antibiotics may be started as empiric antibiotic therapy and continued after the ED visit, either as inpatient or outpatient antibiotic therapy (Trinh and Klinker, 2015; Welch, 2015; May et al., 2021). The use of broad-spectrum antibiotics, however, does not come without risks, especially because they are large drivers of AMR (Laxminarayan et al., 2013; Paharik et al., 2017; Tarrant et al., 2020). They are also likely to cause secondary *Candida* species overgrowth, especially in diabetic patients, and increased incidence of *Clostridium difficile* infection (Czepiel et al., 2019; Mohsen et al., 2020). A qualitative study in the United Kingdom, South Africa and Sri Lanka interviewed prescribers and found that broad-spectrum antibiotics were used due to the perceived high risks of patient deterioration and to avoid peer criticism or litigation (Tarrant et al., 2020). Influenced by senior colleagues and institutional hierarchies, prescribers faced difficulties in challenging established prescribing practices (Tarrant et al., 2020). In South African public hospitals, limited staff, continuity of care issues and patient poverty led to the preference for broad-spectrum antibiotics as a quick and effective treatment to manage complex cases and high patient volumes, and would lead to reduced length of stay at home or in hospital (Tarrant et al., 2020). Extensive investment with regulatory and policy intervention will be needed to solve these suggested drivers of broad-spectrum antibiotic overuse (Cox et al., 2017; Tarrant et al., 2020).

Table 6: Frequencies of the types and classes of antimicrobials prescribed with corresponding diagnoses when used as single agents.

Antimicrobials prescribed	Total, n (%) n= 1251		Corresponding diagnoses*
Antibacterials	**1210**	**(96.7)**	
Penicillin	767	(63.4)	
Amoxicillin/clavulanic acid	684	(89.2)	Abscesses, acute asthma exacerbation, AECOPD, acute gastroenteritis, animal bites, appendicitis bronchitis, burns, catheter-associated UTI, cellulitis, CAP, cholecystitis, complicated leg ulcers, COVID-19, COVID-19 pneumonia, diabetic foot ulcers, dental abscesses, foreign bodies in ear, gastritis, head injuries, Herpes Zoster Ophthalmicus, haemorrhoids, human bites, LRTI, paraphimosis, paronychia, peri-anal abscess, peri-tonsillar abscess, pharyngitis, pressure sores, osteomyelitis, otitis media, renal calculi, scrotal swelling, shingles, sialadenitis, sinusitis, soft tissue injuries, surgical wound infections, syphilis, tonsillitis, URTI, UTI
Intravenous	173	(25.3)	
Oral	511	(74.7)	
Amoxicillin	49	(6.4)	Abscesses, acne vulgaris, CAP, chickenpox, complicated leg ulcers, COVID-19, foreign bodies in eye, head injuries, haemorrhoids, human bites, LRTI, pharyngitis, otitis media, scrotal swelling, soft tissue injuries, tonsillitis
Flucloxacillin	31	(4.0)	Abscesses, burns, cellulitis, complicated leg ulcers, human bite, impetigo, peri-anal abscesses, pharyngitis, soft tissue injuries, tonsillitis
Benzathine benzylpencillin	2	(0.3)	Pharyngitis
Cloxacillin	1	(0.1)	

Table 6: Frequencies of the types and classes of antimicrobials prescribed with corresponding diagnoses when used as single agents continued.

Antimicrobials prescribed	**Total, n (%) n= 1251**		**Corresponding diagnoses***
Macrolides	134	(11.1)	
Azithromycin			Acute asthma exacerbation, acute gastroenteritis, CAP, COVID-19, COVID-19 pneumonia
Intravenous	2	(1.5)	
Oral	132	(98.5)	
Cephalosporins	88	(7.3)	
Ceftriaxone	77	(87.5)	Acute gastroenteritis, animal bites, human bites, AECOPD
Cefazolin	9	(10.2)	Polyarthropathy, callus
Cefuroxime	1	(1.1)	Sepsis at ureteral stent
Cephalexin	1	(1.1)	UTI
Nitroimidazole	85	(7.0)	
Metronidazole			Soft tissue injuries
Fluoroquinolones	57	(4.7)	
Ciprofloxacin			Abscesses, acute gastroenteritis, acute inflammatory diarrhoea, CAP, catheter-associated UTI, haemorrhoids, otitis media, shingles, soft tissue injuries, UTI
Amphenicols	50	(4.1)	
Chloramphenicol			Burns, cellulitis, conjunctivitis, foreign body in eye, head injuries, Herpes Zoster ophthalmicus, keratitis, soft tissue injuries, uveitis
Tetracyclines	20	(1.7)	
Doxycycline	19	(95.0)	GUS, scrotal swelling
Tetracycline	1	(5.0)	
Lincosamides	3	(0.3)	
Clindamycin			Peri-anal abscesses, sialadenitis
Nitrofuran derivatives	3	(0.3)	
Nitrofurantoin			UTI

Table 6: Frequencies of the types and classes of antimicrobials prescribed with corresponding diagnoses when used as single agents continued.

Antimicrobials prescribed	Total, n (%) n= 1251		Corresponding diagnoses*
Aminoglycosides	1	(0.1)	
Gentamicin			
Phosphonic acid derivative	1	(0.1)	
Fosfomycin			UTI
Mupirocin	1	(0.1)	
Antivirals	**26**	**(2.1)**	
Nucleoside and nucleotide analogues	25	(96.2)	
Aciclovir			Shingles, Bell's palsy, Herpes Zoster Ophthalmicus, GUS
Other	1	(3.8)	
Podophyllin			
Antimycotics	**13**	**(1.0)**	
Imidazole derivatives	7	(53.8)	
Clotrimazole	6	(85.7)	Paraphimosis, vaginal candidiasis, GUS
Ketoconazole	1	(14.3)	Fungal rash
Triazole derivatives	4	(30.8)	
Fluconazole			Oral candidiasis, pityriasis versicolor
Polyene antifungal	2	(15.4)	
Nystatin			Oral candidiasis
Antihelmintics	**1**	**(0.1)**	
Benzimidazole	1	(100.0)	
Albendazole			Helminths
Ectoparasiticides	**1**	**(0.1)**	
Benzyl benzoate	1	(100.0)	

Abbreviations: AECOPD: acute exacerbation of chronic obstructive pulmonary disorder; CAP: community-acquired pneumonia; GUS: genital ulcer syndrome; LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection; UTI: urinary tract infection

Note: Not all percentages equal to 100% due to rounding to one decimal; *When used as single agents

Sixty different antimicrobial combinations were identified in this study as displayed in Table 7. The most common combination recorded was amoxicillin/clavulanic acid with azithromycin, followed by the combination of amoxicillin/clavulanic acid with metronidazole, and the combination of ceftriaxone with azithromycin and metronidazole. Amoxicillin/clavulanic acid and ceftriaxone were mostly combined with other antimicrobials.

Table 7: The combination of antimicrobials prescribed in the ED with the corresponding diagnoses.

Combination of antimicrobials prescribed	Frequency	Corresponding diagnoses
Amoxicillin/clavulanic acid + azithromycin	53	Abscesses, AECOPD, acute gastroenteritis, atypical pneumonia, cellulitis, CAP, COVID-19, COVID-19 pneumonia, LRTI, paraphimosis, otitis media, scrotal swelling, sinusitis, URTI
Amoxicillin/clavulanic acid + metronidazole	20	Abscesses, chest pain, dental abscess, human bite, MUS, peri-anal abscess, peritonsillar abscess, soft tissue injury, UTI
Ceftriaxone + azithromycin + metronidazole	18	MUS, PID stage 1, scrotal swelling, STI prophylaxis, VDS
Ceftriaxone + azithromycin + metronidazole + amoxicillin/clavulanic acid	12	MUS, PID stage 1 and stage 2, scrotal swelling, URTI, UTI, VDS
Amoxicillin/clavulanic acid + chloramphenicol	10	Abscesses, category three dog bite, cellulitis, dental abscesses, soft tissue injury
Flucloxacillin + amoxicillin/clavulanic acid	8	Abscesses, cellulitis, head injury, soft tissue injury
Ciprofloxacin + metronidazole	7	Acute gastroenteritis, acute inflammatory diarrhoea, catheter-associated UTI, perianal abscess, UTI
Ceftriaxone + azithromycin + amoxicillin/clavulanic acid	7	AECOPD, CAP, MUS, scrotal swelling
Aciclovir + chloramphenicol	5	Bell's palsy, Herpes Zoster Ophthalmicus

Table 7: The combination of antimicrobials prescribed in the ED with the corresponding diagnoses continued.

Combination of antimicrobials prescribed	Frequency	Corresponding diagnoses
Ceftriaxone + amoxicillin/clavulanic acid	5	Cellulitis, scrotal swelling, TB, UTI
Cefazolin + amoxicillin/clavulanic acid	5	Category three dog bite, popliteal cyst, soft tissue injury
Amoxicillin + metronidazole	4	Dental abscesses, Peptic ulcer disease
Amoxicillin + azithromycin	4	CAP, COVID-19, LRTI
Ceftriaxone + azithromycin	4	Balanitis, CAP, scrotal swelling, tonsillitis
Amoxicillin/clavulanic acid + ciprofloxacin	4	Otitis media, septic arthritis, UTI
Aciclovir + amoxicillin/clavulanic acid + chloramphenicol	4	Herpes Zoster Ophthalmicus, Herpes Simplex Type I
Amoxicillin/clavulanic acid + amoxicillin	3	CAP, LRTI, surgical wound infection
Ceftriaxone + azithromycin + metronidazole + doxycycline	3	MUS, PID stage 1, scrotal swelling
Ceftriaxone + azithromycin + doxycycline	3	Scrotal swelling
Cefazolin + flucloxacillin	2	Osteomyelitis, soft tissue injury
Ceftriaxone + metronidazole + doxycycline	2	PID stage 1
Ceftriaxone + azithromycin + ciprofloxacin	2	Acute inflammatory diarrhoea, CAP
Ceftriaxone + ciprofloxacin	2	Acute gastroenteritis, CAP
Ceftriaxone + azithromycin + amoxicillin/clavulanic acid + doxycycline	2	MUS, scrotal swelling
Ceftriaxone + amoxicillin/clavulanic acid + metronidazole	2	UTI
Amoxicillin/clavulanic acid + flucloxacillin	2	Soft tissue injury, abscesses
Flucloxacillin + podophyllin	1	GUS
Metronidazole + chloramphenicol	1	Animal bite
Amoxicillin/clavulanic acid + cloxacillin + flucloxacillin	1	Abscess

Table 7: The combination of antimicrobials prescribed in the ED with the corresponding diagnoses continued.

Combination of antimicrobials prescribed	Frequency	Corresponding diagnoses
Amoxicillin/clavulanic acid + benzyl benzoate	1	Scabies
Amoxicillin/clavulanic acid + clindamycin	1	Pressure sores
Ceftriaxone + azithromycin + metronidazole + chloramphenicol	1	MUS, GUS, paraphimosis
Amoxicillin/clavulanic acid + tetracycline	1	Peri-anal abscess
Amoxicillin/clavulanic acid + metronidazole + ciprofloxacin	1	Acute gastroenteritis
Ceftriaxone + metronidazole + fluconazole	1	Oral candidiasis
Amoxicillin + chloramphenicol	1	Abscess
Amoxicillin/clavulanic acid + mupirocin	1	Diabetic foot ulcer
Amoxicillin/clavulanic acid + nitrofurantoin	1	UTI
Ciprofloxacin + azithromycin +metronidazole	1	UTI
Amoxicillin/clavulanic acid + flucloxacillin + chloramphenicol	1	Head injury
Ceftriaxone + azithromycin + metronidazole + ciprofloxacin	1	Paraphimosis
Cefazolin + azithromycin + doxycycline	1	GUS
Ceftriaxone + metronidazole + amoxicillin/clavulanic acid	1	UTI
Ceftriaxone + azithromycin + metronidazole + aciclovir	1	Scrotal swelling
Ciprofloxacin + chloramphenicol	1	Stromal abscess and keratitis
Amoxicillin/clavulanic acid + amoxicillin + azithromycin	1	LRTI
Doxycycline + metronidazole	1	Appendicitis

Table 7: The combination of antimicrobials prescribed in the ED with the corresponding diagnoses continued.

Combination of antimicrobials prescribed	Frequency	Corresponding diagnoses
Amoxicillin/clavulanic acid + benzathine benzylpencillin + doxycycline	1	Syphilis
Ceftriaxone + azithromycin + metronidazole + clotrimazole	1	MUS, balanitis, paraphimosis
Azithromycin + nitrofurantoin	1	UTI
Amoxicillin/clavulanic acid + amoxicillin + chloramphenicol	1	Complicated leg ulcer
Amoxicillin/clavulanic acid + metronidazole + gentamicin + doxycycline	1	Human bite
Amoxicillin/clavulanic acid + ceftriaxone + doxycycline	1	Scrotal swelling
Aciclovir + amoxicillin/clavulanic acid + chloramphenicol	1	Herpes Zoster ophthalmicus
Doxycycline + amoxicillin + aciclovir	1	Syphilis
Ceftriaxone + metronidazole + clotrimazole	1	Vaginal candidiasis
Ceftriaxone + azithromycin + ciprofloxacin	1	CAP
Azithromycin + metronidazole	1	MUS
Ceftriaxone + azithromycin + amoxicillin/clavulanic acid + ciprofloxacin	1	UTI
Ceftriaxone + amoxicillin/clavulanic acid + azithromycin	1	AECOPD

Abbreviations: AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; GUS: genital ulcer syndrome; LRTI: lower respiratory tract infection; MUS: male urethritis syndrome; PID: pelvic inflammatory disease; STI: sexually transmitted infection; TB: tuberculosis; URTI: upper respiratory tract infection; UTI: urinary tract infection; VDS: vaginal discharge syndrome

In Almansoori and Parag's (2021) study, amoxicillin/clavulanic acid made up 70.8% of the antimicrobial prescribed, followed by ceftriaxone, cefazolin and cloxacillin. The most common combinations prescribed were amoxicillin/clavulanic acid with azithromycin, and amoxicillin/clavulanic acid with metronidazole. With these similarities, the studies may highlight the common prescribing patterns within South African EDs. There is a high reliance on amoxicillin/clavulanic acid in both mono- and dual antimicrobial therapy. This may only be a trend seen in South Africa. Wang et al. (2016) study in Shanghai, found that cephalosporins were the most frequently prescribed, followed by macrolides, lincosamides and fluoroquinolones. Yi et al. (2022) in Liberia, reported that ceftriaxone made up 28.2% of antimicrobial prescriptions followed by metronidazole (20.5%) and ampicillin (12.5%). In a neighbouring country to South Africa, a study in Botswana revealed that beta-lactam antibiotics made up 45.4% of antibiotic prescriptions, 28.4% of that were amoxicillin prescriptions and only 0.3% were amoxicillin/clavulanic acid (Mashalla et al., 2017). Subsequent to the beta-lactams, the frequently prescribed antibiotics included metronidazole and ceftriaxone. A study in Ivory Coast, however, indicated similar prescribing patterns to this study where amoxicillin/clavulanic acid made up 42.6% of the antimicrobial prescriptions, followed by ceftriaxone at 27.9% (Eric and Serges, 2019). The study also reported similar combinations of amoxicillin/clavulanic acid and metronidazole and amoxicillin/clavulanic acid, ceftriaxone and metronidazole.

The difference in amoxicillin/clavulanic acid usage between South Africa, Botswana, Liberia and Shanghai may be attributed to a number of factors. The South African healthcare system is more developed compared to Liberia's, which continues to face challenges stemming from its post-war recovery, the aftermath of Ebola and scarcer resources (Marston et al., 2017; Dadzie and Kanagasabai, 2022). This may make antibiotics, like amoxicillin/clavulanic acid, less accessible and affordable to the public. Shanghai, however, has stricter regulations around antibiotic prescriptions as China has made efforts to combat AMR (Shen et al., 2022). Physicians may prefer narrower-spectrum antibiotics or in order to follow strict guidelines, reduce the use of broad-spectrum antibiotics like amoxicillin/clavulanic acid (Xia et al., 2019). Although Botswana has an improving healthcare system, it serves a smaller population and fewer urban centres. Limited healthcare access in rural areas may lead to lower antibiotic consumption overall (Mamalelala et al., 2022). The similarity between South Africa and Ivory Coast arises from comparable infectious disease burdens and high HIV rates, which predispose patients to bacterial co-infections (Fofana and Mehmet, 2022). The limited access to advanced diagnostic tools in public healthcare settings in both countries may also be factor as healthcare providers may be led to prescribe broad-spectrum antibiotics in diagnostic uncertainty (Mendelson et al., 2016; Wieters et al., 2024).

Reasons for the higher number of antimicrobials prescribed per patient and use of broader-spectrum antibiotics (such as amoxicillin/clavulanic acid) in this study may be due to the lower-resource settings of these patients. In these settings, there are expected higher burdens of co-morbidities, higher rates of local infections, reduced diagnostic resources and essential medicine shortage (Bosu and Ofori-Adjei, 2000; Ofori-Asenso, 2016; Yi et al., 2022). Infection and complication risk may be increased due to lack of access to clean water and appropriate wound care with sterile materials, which may force the prescribing of antimicrobials (Yi et al., 2022). Prescribing physicians in lower-resource settings may rely on prescribing more than one antimicrobial because they may aim to cover infections empirically. They may also have to rely solely on clinical evaluation as there may be an absence of adequate diagnostic support, the delayed time for results availability and the higher costs associated with culture and sensitivity tests (Anticona Huaynate et al., 2015; Otaigbe and Elikwu, 2023). Studies suggest that the high reliance on amoxicillin/clavulanic acid in South Africa may stem from patients often presenting with advanced stages of illness that prompt physicians to opt for broad-spectrum antibiotics as a precautionary measure. (Krockow and Tarrant, 2019; Tarrant et al., 2021). Another possible reason is the lack of continuity of care and the absence of integrated online record systems. Physicians have to rely on the patient's account of receiving antibiotics during a prior visit to a primary healthcare clinic. Without access to specific details, such as the name of the antibiotic, the physician may have to assume the failure of the initial treatment (Tarrant et al., 2021). The popularity of amoxicillin/clavulanic acid may also be attributed to its long-standing production by national pharmaceutical companies, relatively low cost, bactericidal properties and its availability as oral dosage forms (Schellack et al., 2017; Krockow and Tarrant, 2019).

4.3 Objective 2: Appropriateness of antimicrobials prescribed per prescription in accordance with treatment guidelines using the MAI tool

4.3.1 Overall appropriateness of antimicrobial prescriptions

Antimicrobial prescriptions were deemed overall appropriate if all questions of the modified MAI were marked appropriate or correct according to the respective guidelines. This includes if an antimicrobial was indicated, the choice of antimicrobial, route of administration, strength, frequency, duration, if the directions were complete and practical, if there was no inappropriate duplication of antimicrobial activity and if the antimicrobial therapy was cost-effective. Table 8 displays the overall appropriateness of the antimicrobial therapy study population in the ED, which also includes when antimicrobials were omitted. Of the 850 patient medical charts reviewed with agreement across all three guidelines, only 1.8% (n=15) of the study population received appropriate antimicrobial therapy in the ED and 33.6% (n=286) received inappropriate antimicrobial therapy. In 60 (7.1%) cases the diagnosis was not listed in all three guidelines. The remainder of 57.5% of cases did not have agreement across all three guidelines because of differences in appropriateness of antimicrobial therapy according to the individual guidelines. Excluding the diagnoses not listed (n=60) and the differences in appropriateness assessments between guidelines (n=489), 5.0% were deemed appropriate and 95.0% were inappropriate antimicrobial therapy across all three guidelines. Specifically, only 9.6% of antimicrobial therapies were appropriate according to the STG and EDL guidelines, 8.0% according to the SAASP guidelines, and 10.6% according to the SAMF guidelines (when diagnoses not listed were excluded). A significant portion of the study population, 51.2% (n=435), was excluded from the analysis with the SAASP guidelines because their diagnoses were not listed in the guidelines. This exclusion was anticipated because the SAASP guidelines specifically target conditions requiring antibiotics, omitting viral, fungal or parasitic infections (Wasserman et al., 2014).This was also observed when analysing antimicrobial therapies according to the SAMF. A substantial 52.1% (n=443) of the study population could not be evaluated against these guidelines due to their diagnoses being outside the scope covered. This is because of the SAMF's focus on medication information rather than specific conditions (Rossiter et al., 2016).

Table 8: The appropriateness of the antimicrobial therapy of the study population in the ED in accordance with STG and EDL, SAASP and SAMF guidelines.

	Antimicrobial therapy of the study population		
	n=850		
Treatment guidelines	**Appropriate n (%)**	**Inappropriate n (%)**	**Diagnosis not listed n (%)**
STG and EDL	76 (8.9)	714 (84.0)	60 (7.1)
*Excluding *Diagnosis not listed*	**n=790**		
	76 (9.6)	714 (90.4)	
SAASP	33 (3.9)	382 (44.9)	435 (51.2)
*Excluding *Diagnosis not listed*	**n=415**		
	33 (8.0)	382 (92.0)	

Table 9: The appropriateness of the antimicrobial therapy of the study population in the ED in accordance with STG and EDL, SAASP and SAMF guidelines continued.

Treatment guidelines	Antimicrobial therapy of the study population n=850 Appropriate n (%)	Inappropriate n (%)	Diagnosis not listed n (%)
SAMF	43 (5.1)	364 (42.8)	443 (52.1)
*Excluding *Diagnosis not listed*	n=407		
	43 (10.6)	364 (89.4)	
Agreement between three guidelines	15 (1.8)	286 (33.6)	60 (7.1)
*Excluding *Diagnosis not listed* and differences of appropriateness between guidelines (n=489/850)	n=301		
	15 (5.0)	286 (95.0)	

Many factors need to be taken into account for these low appropriateness percentages. This ED setting is in an academic tertiary hospital that includes practicing intern doctors and medical students. Their knowledge of guideline-specific antimicrobial prescribing may not be as advanced compared to long practicing physicians. Research has shown that physicians with longer experience make better decisions regarding antimicrobial prescriptions (Dooling et al., 2014; Laka et al., 2021). This study did not record the prescriber's position, which could have been compared to the appropriateness of the antimicrobial prescriptions to confirm this supposition. Other factors include the prescribing of antimicrobials in diagnostic uncertainty (Adorka et al., 2013; Laka et al., 2021; Vu et al., 2024). Some physicians may opt to cover the patient with empiric antimicrobials due to a lack of confidence in the decision of the suspected diagnosis. This was evident as 17.2% (n=41/238) of patients with recorded differential diagnoses were provided antimicrobial cover according to one or more of the three guidelines. Again, more work experience reflects better confidence in diagnostic skills and decisions for or against antimicrobial prescriptions. Physicians may also prescribe antimicrobials for the fear of disease complications, particularly in this ED's poorer population (Laka et al., 2021; Vu et al., 2024). Prescribers may perceive that these patients are at higher risk of complications due to the lack of adequate housing, clean water and food supply, adequate nutrition and economic resources (Alothman et al., 2016). There is also a lack of continuity of care as patients may not return for a revisit in this specific ED and the same physician may not be on duty. This may prompt the physicians to prescribe antimicrobials to prevent the wastage of time for the patient (Alothman et al., 2016; Rose et al., 2021). Another factor to consider in this ED is the overcrowding of patients on a daily basis. This ED provides public healthcare to a population of over one million with patients visiting mostly from the centre of the City of Johannesburg, along with other regions such as Roodepoort and Soweto. Although there are many other primary healthcare clinics, hospitals and community healthcare centres in these regions, there is a large daily influx of patients. Overcrowding may put physicians under stress to see as many patients as possible in a single shift and this may take away valuable time in diagnostic work-up which may affect quality of care (Alothman et al., 2016; Laka et al., 2021; Rose et al., 2021; Lagarde and Blaauw, 2023). Public healthcare settings in South Africa are, unfortunately, noted to be short-staffed which adds to the workload of the working physicians. This is common in LMIC healthcare settings. Stock-shortages of the desired antimicrobials may also be a contributing factor (Adorka et al., 2013). This study did not look into the availability of the antimicrobials that should have been prescribed. This can greatly influence the prescriber's decision and they may opt for the readily available antimicrobial (Adorka et al., 2013; Chaw et al., 2018). In such cases, clear communication between prescribers and pharmacists is needed. Pharmacists and prescribers can discuss alternative options for the out-of-stock antimicrobials with the help of microbiologists, to prevent the use of unnecessary broader antimicrobials (Chatterjee et al., 2015; Chaw et al., 2018; Vu et al., 2024). This highlights the need for an AMS committee in this setting, where such discussions can be held.

Table 9 further analyses the appropriateness of antimicrobial therapy by comparing cases where antimicrobials were prescribed to those where they were not, according to each guideline. According to the STG and EDL, only 9.9% of antimicrobial prescriptions were appropriate, whereas only 6.1% of prescriptions without antimicrobials were appropriate. This reveals that in cases where antimicrobials were indicated they were inappropriately omitted. This was also noted in analysis against the SAASP and SAMF guidelines, that 14.3% of prescriptions had antimicrobials appropriately omitted. The analysis found no significant statistical differences in the appropriateness of prescriptions according to the STG and EDL, SAASP and SAMF guidelines, irrespective of whether antimicrobials were prescribed or not ($p=0.306$, $p=0.308$, $p=0.650$; all $p>0.05$). This indicates that the issue of inappropriate antimicrobial prescriptions may extend beyond the use of antimicrobials, suggesting a need for broader improvements in adherence to these guidelines.

Table 10: The appropriateness of the presence or absence of antimicrobial prescriptions in accordance with STG and EDL, SAASP and SAMF guidelines.

Treatment guidelines	Antimicrobials prescribed n=784		Antimicrobials not prescribed n=66		*p*-value
	Appropriate n (%)	Inappropriate n (%)	Appropriate n (%)	Inappropriate n (%)	
STG and EDL*	72 (9.9)	652 (90.1)	4 (6.1)	62 (93.9)	0.306
SAASP*	31 (7.7)	370 (92.3)	2 (14.3)	12 (85.7)	0.308
SAMF*	41 (10.4)	352 (89.6)	2 (14.3)	12 (85.7)	0.650

*Diagnoses not listed in individual guidelines were excluded in percentages

As mentioned before, only 9.6% of antimicrobial therapies were appropriate according to the STG and EDL. This value is considerably lower compared to 45.0% obtained in Gasson, Blockman and Willems' (2018) study conducted in primary healthcare clinics in Cape Town Metro district who only compared against the STG and EDL, however one cannot exclude the difference in study settings. The two South African studies, Gasson, Blackman and Willems (2018) and Almansoori and Parag (2021), researched the prescribing practice of antibiotics in primary healthcare facilities and antimicrobials in the ED with reference to the EDL, respectively. To date, there are no published studies that compared antimicrobial prescribing adherence to the SAASP and SAMF in South African healthcare facilities. The low rates of overall appropriateness of antimicrobial therapy compared to other studies may be due to this study's assessment of duplicate antimicrobial activity, completeness and practicality of the antimicrobial prescription and the cost-effectiveness of the chosen antimicrobials. It is to be noted that antimicrobial therapies that did require more than one antimicrobial where there was overlapping spectrum of activity, such as in the treatments of STIs, were still deemed appropriate because the antimicrobial prescriptions were following the guidelines. In a recent study that used questionnaires to evaluate the utilisation of the STG and EDL and the rational use of medicines among physicians and prescribing nurses reported interesting results (Govender et al., 2021). Only a few prescribers were provided trainings on the STGs and EDL, however, the majority of doctors considered themselves knowledgeable on the use of the STGs and EDL and did not want to receive training on the use of the STG and EDL. The majority of physicians also admitted to only sometimes using the STG and EDL (79.4%), but had more access compared to prescribing nurses, yet nurses scored marginally better than doctors in adherence to guidelines. This may indicate a gap in knowledge of physicians of the current guidelines and provides an area for possible AMS intervention, such as education and continued education amongst prescribers.

Internationally, Grenet et al. (2016) in France, observed that 59.9% of antibiotic treatments were inadequate, with 60.1% due to inadequate antibiotics and 62.9% due to mistakes. Timbrook et al. (2017) also used the MAI tool in the USA and they observed 39% inappropriate antimicrobial prescriptions. Denny et al. study (2019) in Australia, observed a similar result with only 34.2% of inappropriate antibiotic prescriptions. Alanazi et al. study (2015) in Saudi Arabia, observed 46.2% of inappropriate antibiotic prescriptions. Tagashira et al. (2019) in Japan reported that more than half of the antimicrobials were instances of misuse and one third were considered unnecessary. While each of the studies (except for one) differed in assessment tools for prescription appropriateness compared to this study and difference in assessing antibiotic and antimicrobial prescriptions; it is most concerning that the percentage of inappropriateness is double that of other studies' results in other countries. It may reveal a drawback in South Africa's outpatient antimicrobial prescribing practices that urgently needs to be addressed.

4.3.2 Interrater-reliability tests

Overall, interrater reliability of the MAI was high per each guideline ($k > 0.90$) indicating almost perfect agreement. The kappa statistics for the MAI categories per each guideline had almost perfect agreement ($k > 0.90$) except for drug-to-drug interactions and drug-to-disease interactions because kappa statistics could not be calculated for these categories due to the lack of negative agreement.

4.3.3 Appropriateness of Antimicrobial Prescriptions and Treatment Guidelines

Table 10 presents the classification of the assessed prescriptions into the different MAI categories according to each guideline. This representation may help to unpack the areas of improvement needed in antimicrobial prescribing practices.

Table 11: The classification of the prescriptions reviewed in the ED according to the MAI tool under all three guidelines.

MAI categories	STG and EDL n (%)	SAASP n (%)	SAMF n (%)
Indication for an antimicrobial[#]	**n=866**	**n=866**	**n=866**
Appropriate	615 (71.0)	381 (44.0)	379 (43.8)
Antimicrobial indicated and prescribed	613 (99.7)	381	379
Antimicrobial not indicated and not prescribed	2 (0.3)		
Inappropriate	191 (22.1)	39 (4.5)	37 (4.3)
Antimicrobial indicated, but not prescribed	64 (33.5)	14 (35.9)	14 (37.8)
Antimicrobial not indicated, but prescribed	127 (66.5)	25 (64.1)	23 (62.2)
Diagnosis not listed	60 (6.9)	446 (51.5)	450 (52.0)
Choice of antimicrobial *	**n=1000**	**n=623**	**n=630**
Appropriate	387 (38.7)	293 (47.0)	296 (47.0)
Inappropriate	613 (61.3)	330 (53.0)	334 (53.0)
Route of administration **	**n=387**	**n=293**	**n=296**
Appropriate	347 (89.7)	202 (68.9)	167 (56.4)
Inappropriate	38 (9.8)	45 (15.4)	2 (0.7)
Not stated in guidelines	2 (0.5)	46 (15.7)	127 (42.9)
Strength **	**n=387**	**n=293**	**n=296**
Appropriate	312 (80.6)	179 (61.1)	153 (51.7)
Inappropriate	72 (18.6)	55 (18.8)	13 (4.4)
Too low	29 (40.3)	16 (29.1)	9 (69.2)
Too high	43 (59.7)	39 (70.9)	4 (30.8)
Not stated in guidelines	3 (0.8)	59 (20.1)	130 (43.9)
Frequency **	**n=385 [a]**	**n=293**	**n=296**
Appropriate	291 (75.6)	176 (60.1)	142 (48.0)
Inappropriate	91 (23.6)	56 (19.1)	17 (5.7)
Too seldom	57 (62.6)	44 (78.6)	11 (64.7)
Too often	34 (37.4)	12 (21.4)	6 (35.3)
Not stated in guidelines	3 (0.8)	61 (20.8)	137 (46.3)

Table 10: The classification of the prescriptions reviewed in the ED according to the MAI tool under all three guidelines continued.

MAI categories	STG and EDL n (%)	SAASP n (%)	SAMF n (%)
Duration **	**n=378 [b]**	**n=291 [c]**	**n=296**
Appropriate	249 (65.9)	130 (44.7)	128 (43.2)
Inappropriate	120 (31.7)	158 (54.3)	97 (32.8)
Too short	77 (64.2)	115 (72.8)	75 (77.3)
Too long	43 (35.8)	43 (27.2)	22 (22.7)
Not stated in guidelines	9 (2.4)	3 (1.0)	71 (24.0)
Complete and practical directions **	**n=387**	**n=293**	**n=296**
Yes	287 (74.2)	177 (60.4)	130 (43.9)
No	97 (25.1)	56 (19.5)	26 (8.8)
Not stated in guidelines	3 (0.8)	60 (20.5)	140 (47.3)
Drug to drug interactions **	**n=290**	**n=209**	**n=216**
Yes			
No	290 (100.0)	209 (100.0)	216 (100.0)
Drug to disease/condition interactions**	**n=290**	**n=209**	**n=216**
Yes			
No	290 (100.0)	209 (100.0)	216 (100.0)
Inappropriate duplication of antimicrobial activity **	**n=290**	**n=209**	**n=216**
Yes	107 (36.9)	69 (33.0)	75 (34.7)
No	183 (63.1)	140 (66.9)	141 (65.3)
Cost effective antimicrobial therapy **	**n=290**	**n=209**	**n=216**
Yes	142 (49.0)	69 (33.0)	75 (34.7)
No	148 (51.0)	140 (66.9)	141 (65.3)

[#]The indication for an antimicrobial was assessed using the diagnosis recorded by the prescriber and comparing the prescribed treatment to the respective guideline's treatment options

*Only if an antimicrobial was indicated and prescribed

** Only if antimicrobial choice was appropriate

[a] Two prescriptions had the frequency omitted

[b] Nine prescriptions had the duration omitted

[c] Two prescriptions had the duration omitted

4.3.3.1 Indication for an antimicrobial

According to the STG and EDL, the indication for an antimicrobial was appropriate for 71.0% of treated patients (76.3% if excluding diagnoses not listed). This was followed by the SAASP guidelines and SAMF guidelines, of 44.0% and 43.8% respectively. These two guidelines, however, had many diagnoses not listed in the guidelines and if they were to be omitted the percentages would increase to 90.7% (n=381/420) and 91.1% (n=379/416), respectively. This demonstrates that the prescribing physicians made frequent appropriate decisions on whether to prescribe an antimicrobial or not. While the lower percentage of indication appropriateness for STG and EDL guidelines is concerning and shows the need for improvement, it does demonstrate that further education will be built on a general knowledge foundation and prescribing improvements may be seen if interventions are made. It is noted that over 30% of inappropriate prescriptions were due to antimicrobials being indicated for the suspected diagnoses according to guidelines but were not prescribed. This again highlights that prescribers were not effectively following these guidelines. This also highlights risks of untreated infections which may lead to worsening patient outcomes or prolonged illnesses. This also reflects a potential gap in the quality of care provided to patients.

Gasson, Blockman and Willems (2018) reported that 17.1% of patients who received an antibiotic did not require one within the studied primary healthcare clinics in Cape Town. In other words, 82.9% antibiotic indications where adherent to the STG and EDL guidelines. This percentage is higher compared to the present study's result. A higher percentage was also noted in by Skosana et al. (2022) where 89.7% of antimicrobials where prescribed with an appropriate indication in a point prevalence survey with 18 community healthcare centres. In Eric and Serges' study (2019), antibiotic therapy was only considered relevant in 33.59% of cases, although, this study setting lacked local antibiotic therapy guidelines and only assessed relevance from an infectious perspective. From a global perspective, compliance to guidelines for the appropriate indication for antimicrobials ranged from 49% to 81.2% (Timbrook et al., 2017; White et al., 2019; Kiel et al., 2020; Wattengel et al., 2020; García-Moreno et al., 2022). This highlights that this issue is not only present in South Africa as discrepancy in adherence rates across different studies and guidelines emphasises the international challenge of ensuring appropriate antimicrobial use amidst varying healthcare settings and resources. This variability signals the importance of context-specific strategies for AMS, including the development and implementation of localised guidelines, education of prescribers and ongoing monitoring and feedback mechanisms.

4.3.3.2 Choice of antimicrobial

According to the STG and EDL guidelines, 61.3% of the antimicrobial choices were inappropriate. Additionally, the SAASP and SAMF guidelines each reported 53.0% of inappropriate antimicrobial choices. This is alarming as over half of the choices were inappropriate and is a significant risk factor for AMR. This requires urgent attention and education for the prescribing physicians in this ED. This is also concerning because these guidelines are easily accessible to all healthcare professionals in South Africa either through their mobile phones via applications, via the internet or the presence of physical STG and EDL guidelines within the hospital. A South African mobile application, EMGuidance, is also freely available for all healthcare professionals and provides up-to-date information on clinical standards and advancements in medicines, therapeutics and diagnostics (EMG Technologies Proprietary Limited, 2022). This application includes the STG and EDL guidelines that are easily and quickly accessible and provides highly comparable information to the SAMF (EMG Technologies Proprietary Limited, 2022; Mahmood et al., 2023). Despite the accessibility of these resources, compliance with the guidelines among the prescribing physicians in this ED remains notably low. This highlights a critical gap between guideline availability and implementation, and the need for targeted interventions in this area. The percentage of appropriate choice of 38.7% (according to the STG and EDL) was significantly lower compared to Almansoori and Parag's (2021) study, who observed 46.2% of choices were in accordance with these treatment guidelines. Reasons for the difference in percentages may be due to study duration differences, but it is suggestive that prescribing physicians in South African EDs have difficulty in choosing the right antimicrobial. This is highlighted by Gasson, Blockman and Willems (2018), where the incorrect antimicrobial choices made up 11.5% of antibiotic prescription errors.

4.3.3.3 Route of administration

The appropriate route of administration was in 89.7% of antimicrobial prescriptions according to the STG and EDL compared to 68.9% and 56.4% according to SAASP and SAMF guidelines, respectively. If the percentages of those routes not stated in guidelines were omitted, the percentages increase to 90.1%, 81.8% and 98.8% for STG and EDL, SAASP and SAMF guidelines, respectively. While it is promising to see higher percentages of compliance in this prescribing area, it can still be improved upon. This is due to some cases where patients could equally benefit from an oral dose compared to an intravenous dose with resultant cost saving, time-saving and less infection risk to the patient (Boclé et al., 2021; Nguyen et al., 2021; Sendi et al., 2023). This is due to the invasive procedure of inserting a peripheral line for an intravenous infusion that puts patient at risk for injection site infections and includes the added costs of surgical equipment with added waiting time for infusion completion (Dougherty and Lamb, 2008; Li et al., 2019; Indarwati et al., 2020). These values are in range with Eric and Serges' study (2019) where the appropriate route was prescribed in 93.96% of cases. Route of administration is rarely looked at in other published studies similar to the present study but does remain a cost-saving point in AMS interventions.

4.3.3.4 Strength of antimicrobial

This category of the MAI also had higher compliances with prescribed strengths as the adjusted percentages equalled to 81.3% according to the STG and EDL, followed by 76.5% and 92.2% according to SAASP and SAMF guidelines, respectively. Where strengths were inappropriate, most of the strengths were too high according to the STG and EDL, and SAASP guidelines. Inappropriate strengths were mostly considered too low according to the SAMF guidelines. While higher strengths of antimicrobials may be advantageous in AMS strategies, low strengths result in sub-therapeutic serum concentrations of these antimicrobials and is a recognised cause for AMR (Holmes et al., 2016; Gaibani et al., 2021; Bassetti et al., 2022). Another caution to using higher strengths is to avoid toxicity, therefore, prescribing the strength as indicated or researched extensively is best practice.

4.3.3.5 Frequency prescribed

When looking at adjusted percentages, the prescribing of appropriate frequencies fell short, with only 76.1% compliance according to the STG and EDL, with less compliance seen according to SAASP at 75.9%. According to the SAMF guidelines, after adjusting omitted frequencies in guidelines, compliance is the highest at 89.3%. Frequencies that were inappropriate were mostly prescribed too seldom. This is concerning because while the strength of the antimicrobial may be correct, the patient may be receiving less of what is necessary to treat the infection. This especially affects antimicrobials that are time-dependent (Eyler and

Shvets, 2019). This may also be a driver of AMR and education for these prescribers is urgently needed (Holmes et al., 2016; Bassetti et al., 2022).

Numerous studies have focused on comparing the dosage of antimicrobials rather than their strength or administration frequency, underscoring the unique contribution of this research. Gasson, Blockman and Willems (2018) identified that incorrect antibiotic dosages constituted 12.9% of all prescribing errors. Conversely, Almansoori and Parag (2021) revealed a much higher rate of accurately prescribed doses, at 92.8%. Eric and Serges' study (2021) aligned with this study's findings, indicated that only 70.57% of antimicrobial prescriptions were compliant in terms of dosage. In contrast, within the USA, Timbrook et al. (2017) reported a notably lower incidence of inappropriate dosing, at just 1.3% of prescriptions, whereas White et al. (2019) found that incorrect dosages accounted for 18.7% of prescriptions. Given the regional variations observed, it is evident that dosing practices present a potential target for intervention.

4.3.3.6 Treatment duration

After adjusting for durations not stated in the guidelines, only 67.5% of the prescribed treatment durations were appropriate according to the STG compared to 45.1% and 56.9% according to SAASP and SAMF guidelines, respectively. The observed trend was that frequencies were often too short rather than too long. Again, this is concerning because the patient may be stopping the antimicrobial too soon where a longer course may be indicated. Research, including studies by Dawson-Hahn et al. (2017) and Hanretty and Gallagher (2018), suggests that shorter antibiotic courses might not negatively impact patient outcomes or the time to clinical cure. Any decision, however, to reduce the length of antimicrobial treatments must be backed by published literature. Treatment guidelines are established to reflect the newest evidence-based recommendations for managing prevalent conditions in specific regions, emphasising the importance of adhering to these guidelines to ensure optimal patient care. The study in primary healthcare clinics by Gasson, Blockman and Willems (2018) revealed that incorrect treatment durations was the fifth reason for antimicrobial prescription errors. This may be considered a universal weakness for prescribers because several studies have also reported low compliance. The study by Timbrook et al. (2018) reported that 5% of antimicrobial prescriptions had inappropriate treatment durations, while White et al. (2019) reported a higher percentage of 24,6%. Grenet et al. (2016) found inadequate treatment duration was noted in 28% of antimicrobial prescriptions, with 18% being too long.

4.3.3.7 Complete and practical directions

The prescribed directions were mostly complete and practical with 74.2% compliant according to the STG and EDL, and 60.4% and 43.9% according to SAASP and SAMF guidelines, respectively. When excluding cases where directions were not stated, the compliance increased to 76.0% for SAASP and 83.3% for SAMF guidelines. This suggests that detail may not be considered when prescribing antimicrobials in these cases and it needs to be emphasised to prescribers. It also highlights the possible limitation of the SAASP and SAMF guidelines and improvements need to be made to add finer details to the antimicrobial prescribing directions. This present study uniquely assessed the appropriateness of the prescribed directions with regards to completeness and practicality. In the raw data, a common reason for incomplete directions was the prescribed directions of aciclovir where the prescribers wrote “take five times a day”, but according to guidelines it should also state “take 4 hourly missing the midnight dose” (Rossiter et al., 2016; National Department of Health, 2020). A simple addition to their instructions would have made it easier for the patient to understand how to take their medicines. It may be the case that the prescribers expect the pharmacist to counsel the patient efficiently or to add these instructions on their own accord, but in public healthcare settings where there are time constraints and large population demands, these small details may be missed without a written reminder. While there is limited data to compare to, these findings do suggest that prescribers should take more care in their instructions to make it easier for their patients to understand.

4.3.3.8 Inappropriate duplication of spectrum of antimicrobial therapy

While it is promising that inappropriate duplication of spectrum of antimicrobial therapy was less than 40% according to the different guidelines, it is, however, still important to monitor because over 40% of patients received more than one type of antimicrobial. Ideally, the combination of antimicrobials should be reserved for specific instances and the risk of unnecessary combinations is the increased exposure of microorganisms to these antimicrobials, driving AMR (Levy-Hara et al., 2011; Tomas and Aljadeeah, 2022). Unnecessary duplication of antimicrobials also leads to increase in costs and risk of side effects (Levy-Hara et al., 2011; Tomas and Aljadeeah, 2022). Across all guidelines there was a consensus of the unnecessary duplication of antibiotic activity between amoxicillin/clavulanic acid or amoxicillin and azithromycin for CAP (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b). This, however, speaks to the prescribing practice of these doctors that they would rather have the patient take the azithromycin as a comprehensive treatment coverage instead of being forced to come back after 48 hours if there was clinical deterioration or to go to another healthcare setting, such as a clinic (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b). In defence of the prescribers, however, there are international guidelines that opt for the amoxicillin/clavulanic acid and macrolide combination in moderately severe CAP, possibly indicating an update is needed of South African guidelines (Metlay et al., 2019; National Institute for Health and Care Excellence, 2019). Another instance of prescribing full antimicrobial coverage was when doctors prescribed ceftriaxone, azithromycin and metronidazole for male urethritis syndrome (MUS). Metronidazole is only indicated if the partner has vaginal discharge syndrome (VDS) as per the STG and EDL, but in all cases, this was not recorded and the doctors may have opted to prescribe the metronidazole because of patient's partner's unknown medical and/or sexual history (National Department of Health, 2020). While this did not affect the number of inappropriate duplications of antimicrobial activity for the STG and EDL guidelines, it did affect the SAASP and SAMF values, as the metronidazole is not listed in these guidelines for this purpose (Wasserman et al., 2014; Rossiter et al., 2016). This now highlights another issue where there are some obvious differences between guidelines, therefore, a concentrated effort should be made to make a general, evidence-based consensus on these guidelines. This is difficult because different organisations are involved with each of the guideline development and, for example in this case, to get all three organisations to set up open meetings or communications could prove to be challenging and time consuming. The factors that influence the prescribing of unnecessary antimicrobial combinations is not well studied, but a study in China revealed that doctors who are more knowledgeable of antimicrobials were less prone to prescribing combinations (Wushouer et al., 2020; Tomas and Aljadeeah, 2022).

4.3.3.9 Cost-effective antimicrobial therapy

It is concerning that the cost-effectiveness of the antimicrobial therapy was a low scorer, especially because in limited-resource settings one should be observant to one's expenditure. According to the STG and EDL, 49.0% of the prescribed antimicrobials were the most cost-effective compared to 28.2% and 30.6% according to SAASP and SAMF guidelines, respectively. This indicates that over half of the antimicrobial prescriptions with at least one appropriate antimicrobial prescribed, were not cost-effective. While in this case it does not financially cost the patient, it does cost the state and indicates an important area to target interventions. There were a few ways to improve the cost-effectiveness of the prescribed antimicrobial therapy. This includes prescribing the oral instead of the intravenous formulations, along with choosing the first-line antimicrobial, avoiding duplicate spectrum cover when it is not indicated and ensuring that the appropriate frequency, strength and treatment duration are prescribed. This is where ensuring appropriate prescribing has economic benefit and has been extensively researched (Dixon and Duncan, 2014; Gordon et al., 2023). In reference to other studies, Timbrook et al. (2017) reported that only 7.5% of all antimicrobial prescriptions were more expensive than recommended treatment.

4.3.4 Appropriateness of Antimicrobial Prescriptions and Diagnoses

Table 11 displays the overall appropriateness of the antimicrobial therapy for the most frequent condition categories and diagnoses according to the specific guidelines. It is concerning that most of the conditions, across all three guidelines were treated inappropriately. According to the STG and EDL of the most frequent condition categories, trauma and injuries were most appropriately treated compared to urinary tract conditions and skin and soft tissue conditions which were mostly inappropriately treated. Conversely, according to the SAASP the skin and soft tissue conditions were the most appropriately treated and trauma and injuries were most inappropriately treated. The most appropriately treated condition category was lower respiratory tract conditions according to the SAMF guidelines, with trauma and injuries being the most inappropriately treated. It must be taken into account, however, that the SAASP and SAMF have limited trauma and injury condition treatment guidelines. Figure 4 displays the distribution of the different categories for inappropriate antimicrobial prescriptions for each of these most frequent condition categories. According to this display, the most frequent reasons for inappropriateness are highlighted and include the inappropriate choice of the antimicrobial, treatment duration, duplication of antimicrobial activity and poor cost-effectiveness of the prescribed antimicrobial therapy. These reasons for inappropriateness are also seen across all three guidelines, highlighting where AMS interventions are needed.

4.3.4.1 Skin and soft tissue conditions

A large percentage of skin and soft tissue conditions were inappropriately treated (89.7% to 95.4%). In respect of treating skin and soft tissue conditions, prevalent issues have been identified by the guidelines that highlight key areas for improvement in antimicrobial prescriptions. The choice of antimicrobials, the cost-effectiveness antimicrobial therapy options and the treatment durations stand out as critical concerns. Another issue underscored is the lack of providing clear, practical directions. These findings pinpoint where prescriber training and education should focus for further benefit. Gasson, Blockman and Willems (2018) reported a similar distribution of reasons for non-adherence to the EDL for dermatological conditions, although 65.6% of antimicrobial prescriptions were adherent. The findings were that 22.6% of errors were due to incorrect drug choices, 15.1% were incorrect treatment durations and 9.4% were due to the antibiotic not being indicated. Other studies reported a range of 20.1% to 74.4% of appropriate antimicrobial treatments for SSTIs (Alanazi et al., 2015; Grenet et al., 2016; Fahs et al., 2017; Timbrook et al., 2017; Kamath et al., 2018).

Abscesses made up a large portion of the skin and soft tissue diagnoses and was poorly managed as 93% and 94.8% of antimicrobial treatments were inappropriate per STG and EDL and SAASP, respectively. This was due to amoxicillin/clavulanic acid being prescribed when flucloxacillin was indicated according to the STG and EDL and, while amoxicillin/clavulanic acid was indicated according to SAASP, it was least cost-effective compared to flucloxacillin (Wasserman et al., 2014; National Department of Health, 2019b, 2020). Pus aspirate specimens cultured *S. aureus* (n=5), *S. hominis* (n=1) and *S. pyogenes* (n=1), which were susceptible to flucloxacillin. Although the sample was small, this further suggests that the broader amoxicillin/clavulanic acid was not necessary. It is also important to note that 40% of the pus aspirate specimens did not culture any microorganisms (but were prescribed antibiotics) which also highlights that incision and drainage would have been more appropriate first-line management and antibiotics were not necessary (National Department of Health, 2020). Kamath et al. (2018) also observed a high incidence of inappropriate antimicrobial choices, noting that 45% of abscess cases were treated with an incorrect antimicrobial. There are a limited number of studies that assess appropriateness for antimicrobial prescriptions for abscesses, but some studies have aimed to determine possible AMS interventions. Studies conducted by May et al. (2021) and Ebied and Antonelli (2022) implemented AMS interventions to improve antibiotic prescribing for SSTIs such as prescriber education, implementation of a clinical treatment algorithm, electronic order set, an institution formulary, institution antibiogram and audit and feedback. May et al. (2021) reported a modest improvement to guideline adherence, whereas Ebied and Antonelli (2022) reported rates as per pre-intervention group. Future research should look into the factors for inappropriate

Table 12: Overall appropriateness of treatments in the most frequent condition groups and diagnoses according to the specific guidelines.

Condition group	Total n (%)	STG and EDL Appropriate treatment n (%)	STG and EDL Inappropriate treatment n (%)	*p*-value	SAASP Appropriate treatment n (%)	SAASP Inappropriate treatment n (%)	*p*-value	SAMF Appropriate treatment n (%)	SAMF Inappropriate treatment n (%)	*p*-value
Skin and soft tissue conditions	171 (19.8)	11 (6.7)	152 (93.3)	0.150	12 (10.3)	105 (89.7)	0.268	3 (4.7)	61 (95.3)	0.090
Trauma and injuries	166 (19.2)	25 (15.1)	141 (84.9)	**0.012**		19 (100.0)	0.385		5 (100.0)	1.000
Lower respiratory tract conditions	136 (15.7)	8 (7.1)	105 (92.9)	0.304	6 (7.9)	70 (92.1)	0.989	9 (10.8)	74 (89.2)	0.926
Urinary tract conditions	106 (12.2)	7 (6.7)	97 (93.3)	0.267	9 (9.0)	91 (91.0)	0.650	8 (7.9)	93 (92.1)	0.319
Reproductive system conditions	97 (11.2)	8 (8.5)	86 (91.5)	0.637	1 (3.7)	26 (96.3)	0.711	3 (6.5)	43 (93.5)	0.451
Diagnosis										
UTI	92 (10.6)	5 (5.4)	87 (94.6)	0.421	8 (8.7)	84 (91.3)	0.765	7 (7.6)	85 (92.4)	0.225
Animal bites	71 (8.2)	19 (26.8)	52 (73.2)	**<0.0001**						
CAP	66 (7.6)	5 (7.6)	61 (92.4)	0.505	6 (9.1)	60 (90.9)	0.685	9 (13.6)	57 (86.4)	0.421
Abscesses	58 (6.7)	4 (6.9)	54 (93.1)	0.423	3 (5.2)	55 (94.8)	0.599			
Soft tissue injuries	49 (5.7)		49 (100.0)	**0.011**		4 (100.0)	1.00		3 (100.0)	1.00

Abbreviations: CAP: community-acquired pneumonia; UTI: urinary tract infection

Note: $p<0.05$ is in bold, values where the diagnosis was not listed are excluded on the table and in percentage calculations; statistical analysis was conducted between the appropriate and inappropriate antimicrobial treatment per each category within each guideline.

prescribing in SSTIs, including abscesses, to address the poor of adherence to guidelines (May et al., 2021).

4.3.4.2 Trauma and injuries

In the context of managing trauma and injuries, the STG and EDL guidelines highlight several issues with antimicrobial prescriptions, starting with the inappropriate decision-making regarding whether to prescribe an antimicrobial at all. Further reasons for inappropriateness were closely followed by concerns over the choice of antimicrobial and the duration of treatment. The SAASP guidelines echo this, emphasising that the primary challenge lies in the decision to prescribe or not to prescribe antimicrobials, with the choice of antimicrobial also being a significant concern. Meanwhile, the SAMF guidelines point to the choice of antimicrobial as the sole issue.

Animal bites and soft tissue injures were commonly encountered, but also acquired high rates of inappropriate antimicrobial prescriptions. Antimicrobial prescriptions for soft tissue injuries were 100% inappropriate across all three guidelines and 73.2% for animal bite prescriptions according to the STG and EDL. Other diagnoses were human bites, head injuries and burns. Many hospitals commonly administer prophylactic antibiotics for treating traumatic injuries despite numerous current treatment guidelines advising against their routine use. In this study it was observed that amoxicillin/clavulanic acid was prescribed as antibiotic prophylaxis following soft tissue injuries, head injuries and burns when it is not indicated in the STG and EDL. Clear guidelines or specific criteria for antibiotic prophylaxis in trauma cases are still not well-defined, especially in the South African STG and EDL. A recent study by Coccolini et al. (2024) aimed to describe the indications of antibiotic prophylaxis in traumatic lesions endorsed by published guidelines. The authors stated that patients with blunt head and brain trauma treated non-operatively do not require antibiotic prophylaxis, as there are no significant differences in infection rates between those who received antibiotic prophylaxis and those who did not. The authors also reported that routine antibiotic prophylaxis for skin and soft-tissue injuries is not always recommended and should be evaluated on a case-by-case basis, as well as routine antibiotic prophylaxis in non-severe burns is not indicated. Another study attempted to create a clinical practice guideline on prophylactic antibiotics for adults with fresh traumatic wounds. In this guideline, antibiotic prophylaxis was indicated in clean-contaminated and contaminated fresh traumatic wounds. The authors reported that despite the presence of this

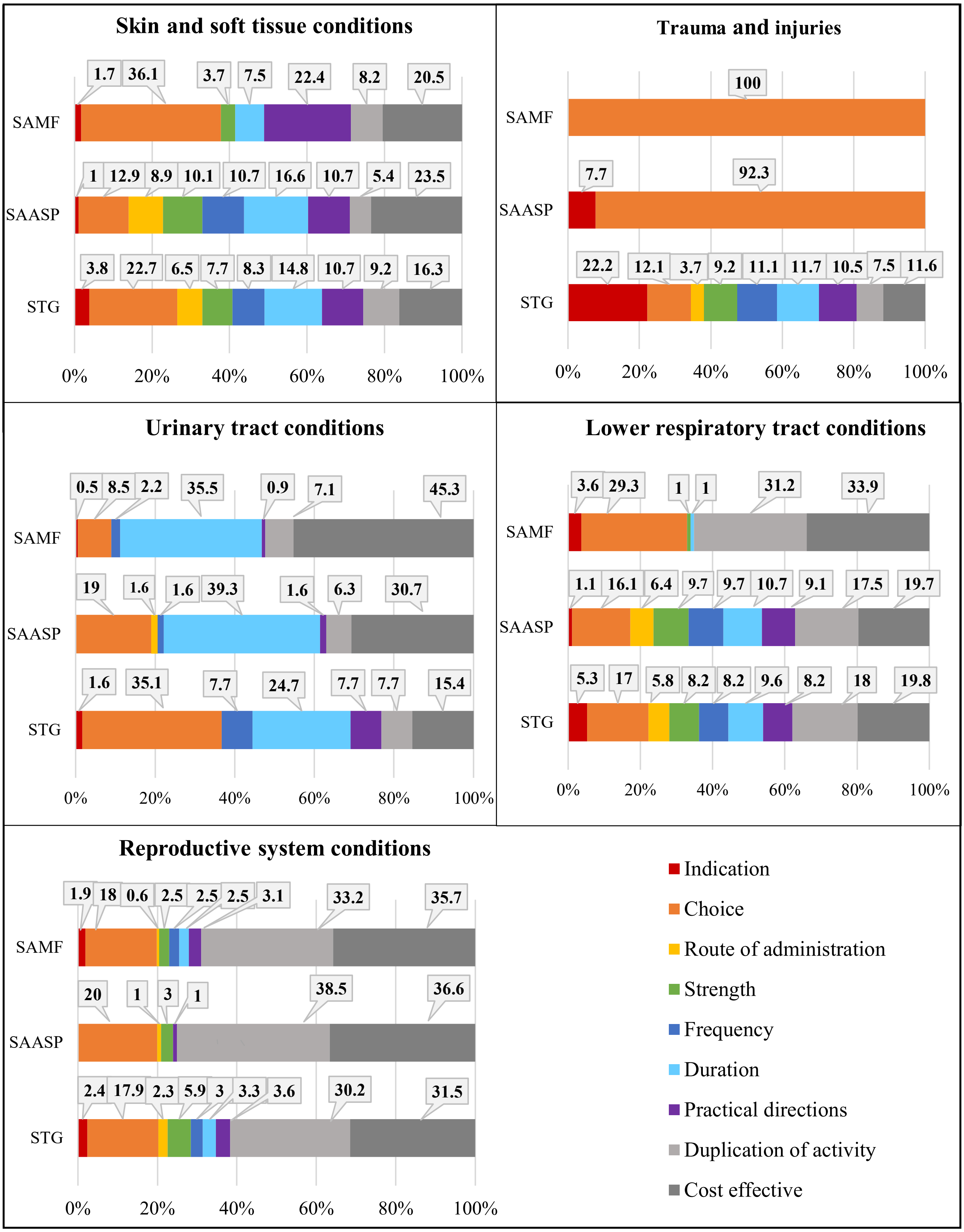

Figure 4: Bar graphs showing the distribution of categories of inappropriateness for antimicrobial prescriptions in the most frequent categories of conditions.

institution-specific guideline, only 40.5% of patients received treatment according to recommendations (Sirijatuphat et al., 2015). Clearer guidelines on the use of prophylactic antibiotics for traumatic injuries would be advantageous, particularly in the South African context, where trauma due to interpersonal violence, self-inflicted injury, collective violence, and unintentional injuries is prevalent (Pillay et al., 2012; Schuurman et al., 2015; Zaidi et al., 2019).

Common reasons for inappropriate treatment for animal bites were due to duplication of spectrum of antimicrobial activity (combination of metronidazole and amoxicillin/clavulanic acid) and omitting an antimicrobial when it was indicated for a category three bite or exposure (classified as bites or scratches that penetrate the skin and with any visible blood and/or licking of broken skin or mucous membranes such as the eyes or mouth) (National Department of Health, 2020). This was similarly observed in the study of Birdsey et al. (2016) where only 61.9% of animal bite treatments adhered to guidelines. Antibiotic choices were non-adherent to guidelines in 18.7% of cases and 11.9% of cases had antibiotics omitted when they were indicated. A local retrospective audit study of medical records of patients visiting the ED with dog-bite wounds reported that the most common antibiotic prescribed was cloxacillin, followed by amoxicillin, amoxicillin/clavulanic acid and metronidazole. Comparing this to the current STG and EDL guidelines, only the amoxicillin/clavulanic acid was acceptable antimicrobial therapy (unless metronidazole and azithromycin was used in presence of a penicillin allergy) (National Department of Health, 2020). The inappropriate management of these animal bites may be attributed to unfamiliarity with guidelines and/or spectrums of activities of antimicrobials. Educational interventions may be useful where guideline revision and treatment algorithms are used, a topic for future research.

4.3.4.3 Urinary tract conditions

In managing urinary tract conditions, noncompliance with the STG and EDL guidelines stemmed from an inappropriate selection of antimicrobials, along with treatment duration and poor cost-effectiveness. The SAASP guidelines echo this pattern, placing treatment duration as the foremost reason for noncompliance, closely followed by challenges in achieving cost-effectiveness and in the selection of antimicrobials. This trend is similarly observed in the SAMF guidelines, where treatment duration, cost-effectiveness and antimicrobial choice are highlighted as the key areas of concern. Urine specimens mostly cultured *E. coli* in patients diagnosed with UTIs and *P. mirabilis* in one patient diagnosed with a catheter-associated UTI (Appendix G). Most choices were inappropriate purely based on microorganism susceptibility. In the STG, for females of child-bearing age who are immunocompetent diagnosed with uncomplicated cystitis the first-line antibiotic options are gentamicin, fosfomycin and nitrofurantoin (National Department of Health, 2020). In the sample displayed it is clear that gentamicin and nitrofurantoin were better options compared to amoxicillin/clavulanic acid. This highlights the STG guidelines are reliable and up to date with microorganism susceptibilities in this patient population and should be followed, but unfortunately were not except in one patient. The one specimen cultured *P. mirabilis* in a patient diagnosed with catheter-associated UTI was resistant to ciprofloxacin, which was appropriately prescribed according to guidelines (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b, 2020). This indicates that either an update is needed in the guidelines with regards to this patient population or the ED needs to generate antibiograms for this condition to optimise the antibiotic therapy. Gasson, Blockman and Willems (2018) also reported that incorrect treatment durations were highest for urological conditions. This was followed by the incorrect drug choice, which mirrors this study. High percentages of inappropriate antimicrobial prescriptions are recorded in this study with 94.6%, 91.3% and 92.4% according to the STG and EDL, SAASP and SAMF, respectively. Studies from other countries also indicate that incorrect treatment duration and antibiotic choice for UTIs is a common issue. White et al. (2019) reported 45.1% incorrect drug choices and 47.1% incorrect treatment durations and Wattengel et al. (2020) also reported somewhat similar results with 50.9% of incorrect durations and 35.1% of incorrect antibiotic choices. Other studies also reported a range of 25% to 63.1% of non-adherent antimicrobial prescriptions overall (Alanazi et al., 2015; Grenet et al, 2016; Fahs et al., 2017; Timbrook et al., 2017). Taking this all into consideration, possible targets for AMS interventions would be to improve knowledge of local guidelines through education and monitor prescribing patterns on a continuous basis for UTIs (Keuler et al., 2022).

4.3.4.4 Lower respiratory tract conditions

For lower respiratory tract conditions, noncompliance with the STG and EDL guidelines is primarily attributed to the lack of cost-effectiveness in treatments, which is closely followed by issues such as unnecessary duplication of antimicrobial spectrum of activity and the inappropriate selection of antimicrobials. This pattern of noncompliance was consistently reflected when compared to the SAASP and the SAMF guidelines. This indicates a common prescribing practice in these specific conditions. Only one sputum specimen was taken and grew *C. albicans* which is commonly part of oropharyngeal flora (Patel, 2022). The percentages of inappropriateness for the antimicrobial prescriptions ranged from 89.2% to 92.9%. Community-acquired pneumonia was commonly diagnosed but had high rates of inappropriate antimicrobial prescriptions ranging from 86.4% to 92.4%. This range is much higher than previously reported 30.8% to 71.7% (Fahs et al., 2017; Timbrook et al., 2017; Wattengel et al., 2020). Wattengel et al. (2019) reported that that the reasons for inappropriate antibiotic regimens were due to 76.7% of incorrect antibiotic choices, 39.4% of incorrect durations and 5.1% of incorrect doses, similarly seen in this study. The authors also reported that azithromycin accounted for 64% of inappropriate antibiotic selection. As previously mentioned, the combination of amoxicillin/clavulanic acid and azithromycin is a prescribing practice in this ED and future AMS intervention should focus on managing the attitudes and beliefs of prescribers in order to prevent full antimicrobial coverage prescribing when it is not indicated. Another area for improvement would be to improve knowledge of guidelines because some patients may only require amoxicillin instead of amoxicillin/clavulanic acid depending on their medical history (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b, 2020).

4.3.4.5 Reproductive system conditions

In addressing reproductive system conditions, the STG guidelines point out that the primary challenges leading to noncompliance involve poor cost-effectiveness, which precedes concerns of unnecessary duplication of antimicrobial activity and inappropriate choice of antimicrobials. This pattern is mirrored in the SAASP and SAMF guidelines for these conditions. Inappropriate antimicrobial prescriptions ranged from 91.5% to 96.3%. This range is much higher than 35.6% reported by Gasson, Blockman and Willems (2018). As previously mentioned, a common reason for inappropriate antimicrobial prescriptions was due the addition of metronidazole in MUS treatments. It was also observed that many of the syndrome treatment combinations were not followed as per the guidelines. This may be due to the unfamiliarity of the antibiotic combinations or the prescribers trying to overlap syndrome managements. A local study conducted in two correctional centres with primary healthcare facilities showed variable compliance rates for combined treatment of specific STIs according to the STG and EDL (Matsitse et al., 2017). Compliance for MUS was 75.9%, while it was only 11.4% for lower abdominal pain and 14.9% for GUS prescriptions (Matsitse et al., 2017). The study also reported that sometimes prescribers did not prescribe appropriate treatment durations, frequency and dosages. The need for regular training on current guidelines is suggested to improve compliance.

4.3.5 Appropriateness of Prescribed Antimicrobials

Figure 5 shows the breakdown of various categories leading to inappropriate prescriptions for each of the most prescribed antimicrobials. These graphs highlight the most common reasons for inappropriateness, such as the inappropriate choice, along with issues related to the route of administration, strength, frequency and duration of treatment. The fact that these reasons for inappropriateness are observed across all three guidelines underscores the need for AMS interventions.

The primary and most concerning cause of inappropriate antimicrobial prescriptions is the incorrect selection according to the guidelines. This is observed more frequently in azithromycin (64.5% to 89.6%) and ceftriaxone (43.2% to 78.3%) prescriptions, followed by metronidazole, ciprofloxacin and amoxicillin/clavulanic acid (19.5% to 68.1%) compared to other prescribed antibiotics. Another common cause is due to the inappropriate treatment duration. This was mostly observed in ciprofloxacin prescriptions (44.2% to 61.4%), but also noted in metronidazole and amoxicillin/clavulanic acid prescriptions (17.3% to 31.9%). Inappropriate strengths and frequencies were other common causes observed in nearly all five of these antimicrobial prescriptions.

A few studies have observed inappropriate amoxicillin/clavulanic acid prescriptions. Birdsey et al. (2016) observed that amoxicillin/clavulanic acid was prescribed for low-risk animal bites when it was not indicated and White et al. (2019) and García-Moreno et al. (2022) observed that some amoxicillin/clavulanic acid prescriptions had inappropriate treatment durations and some with inappropriately prescribed strengths. Grenet et al. (2016) reported that 74.28% of amoxicillin/clavulanic acid prescriptions were inadequate and had similar observations of amoxicillin/clavulanic acid being prescribed when another agent was more suitable and recognised by guidelines, such as amoxicillin for cutaneous infections. The authors recognise the risk of using this broad-spectrum antibiotic because of the associated risk of extended-spectrum beta-lactamase-producing bacteria selection. Regardless of this risk, they are still frequently prescribed in outpatient settings.

In this study, amoxicillin/clavulanic acid was prescribed regularly for a wide range of diagnoses, but inappropriately for abscesses, soft tissue injuries, UTIs and ENT infections according to the STG and EDL. In these cases, amoxicillin/clavulanic acid could have been replaced by flucloxacillin or amoxicillin, which would have been more cost-effective. The SAASP and SAMF recognises the indication of amoxicillin/clavulanic acid for abscesses and UTIs, however, it is not recorded as first-line. Grenet et al. (2016) suggested to tackle this dilemma by ensuring protocols are designed and available for ED settings for infectious diseases. Details, such as treatment duration, should be available on these protocols and distributed to all prescribers. In the South African context, prescribers can access guidelines easily through mobile applications (such as EMGuidance) or the STG and EDL book available in the ED, therefore, access is not the issue. Training of these prescribers could be more beneficial along with posters or visual aids present in areas where prescriptions are written and sharing of antibiograms regularly (Buising et al., 2008; May et al., 2021; Sapozhnikov et al., 2024). Another suggestion is to restrict access to amoxicillin/clavulanic acid (Matanovic et al., 2010; Van Den Broek et al., 2020). A study conducted in Netherlands in three hospital outpatient clinics reported that amoxicillin/clavulanic acid was regularly prescribed, but often inappropriately (Van Den Broek et al., 2020). It is concerning that a number of studies globally have observed this occurrence (al Salman et al., 2015; Ali et al., 2021; Ferre-Sanfrancisco et al., 2023).

Azithromycin was frequently inappropriately selected as drug of choice in combination with amoxicillin/clavulanic acid for CAP. According to the STG and EDL, SAASP and SAMF, the recommendation is that azithromycin is to be added when patient returns after 48 hours after receiving amoxicillin or amoxicillin/clavulanic acid (National Department of Health, 2019b; Rossiter et al., 2016; Wasserman et al., 2014). This again shows prescribers concerns over patients' constraints that would make it difficult to return mentioned previously. Azithromycin was also inappropriately combined with a number of different antibiotics for various ear, nose and throat infections. A study conducted in a paediatric ED identified that azithromycin was inappropriately prescribed with amoxicillin/clavulanic acid for CAP while amoxicillin was treatment of choice (Ferre-Sanfrancisco et al., 2023). The authors also reported the inappropria-

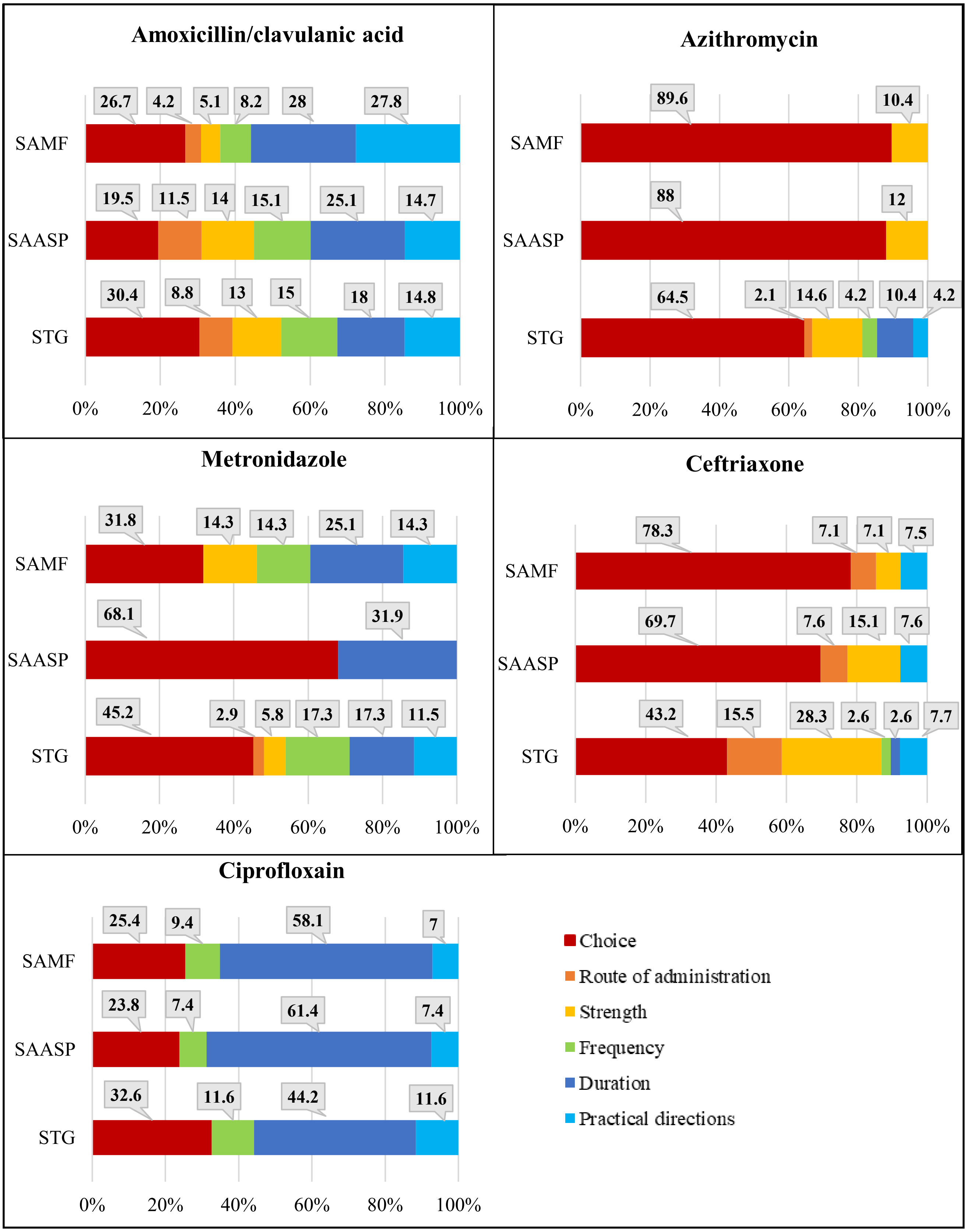

Figure 5: Bar graphs showing the distribution of categories deemed inappropriate for the most frequently prescribed antimicrobials.

-te combination of azithromycin and amoxicillin/clavulanic acid for acute pharyngitis and tonsillitis. The inappropriate use in CAP was documented in another study, where azithromycin accounted for 64% of inappropriate antibiotic selections for this diagnosis (Wattengel et al., 2019).

Metronidazole was chosen inappropriately for a number of cases such as an additive agent with amoxicillin/clavulanic acid for human bites, soft tissue injuries and MUS, when partners have indicated VDS according to the STG and EDL. These inappropriate combinations resulted in a duplication of anaerobic coverage and unnecessarily increases expenditure. Grenet et al. (2016) reported that 100% of metronidazole prescriptions were inadequate. It is suggested that prescribing metronidazole when there is no evidence of anaerobic infection leads to risk of neurological side effects, disruption of normal human flora within the body and increasing *Bacteroides fragilis* resistance (Trienski and Bhanot, 2022; Mo et al., 2023). Further reasons for inappropriate metronidazole prescriptions were due to inappropriate treatment duration and strength. This was frequently seen in treatment for STIs. Possible AMS interventions suggested is the prospective review and feedback of antimicrobial prescriptions in this case, as education is not adequate alone, but may prove to be difficult in an ED or outpatient setting (Barlam et al., 2016; Trienski and Bhanot, 2022).

Ceftriaxone was frequently selected inappropriately, followed by incorrect strength and route of administration in prescriptions. In a systematic review of ceftriaxone use in Sub-Saharan Africa revealed that three in five patients received inappropriate ceftriaxone dose, frequency or duration with higher inappropriate rates compared to a study conducted in the USA (Fleming-Dutra et al., 2016; Bishaw et al., 2021). The inappropriate selection is a major contributor and is also highlighted by Gennai et al. (2018) where 12.8% of ceftriaxone choices were not relevant. Another concern is the inappropriate route of administration. In these cases, the physicians would prescribe the intravenous, not the intramuscular route. A possible reason for this change is due to the pain caused by the intramuscular injection of ceftriaxone, but the intravenous route comes with its own risks as previously mentioned.

Interestingly, ciprofloxacin prescriptions mostly had inappropriate treatment durations. This was mainly due to the variance of treatment durations between uncomplicated and complicated

UTIs (three days versus seven days) (Wasserman et al., 2014; Rossiter et al., 2016; National Department of Health, 2019b, 2020). This was similarly observed by Gasson, Blockman and Willems (2018) who reported that ciprofloxacin had the least adherence rate to the primary healthcare EDL and it was mainly due to incorrect treatment durations. This may be common issue because a number studies globally have reported similar issues (Durkin et al., 2018; Kabbara et al., 2018; Feroche and Alemu, 2021). A study conducted in an American ED and ambulatory care centre reported that only 5.2% of ciprofloxacin prescriptions had appropriate duration of treatment prescribed for uncomplicated cystitis (Natali and Nerenberg, 2021). To combat this issue, an in-service training was conducted with staff and the authors developed an institution-specific guideline for the empiric treatment for uncomplicated cystitis (Natali and Nerenberg, 2021).

4.4 Summary of results

4.4.1 Objective 1: To determine the antimicrobial prescribing patterns of prescribing physicians in the ED of Helen Joseph Hospital

- Antimicrobial prescriptions were similarly distributed across sex, age, presence of co-morbidities and chronic medicines as displayed in Figure 6.

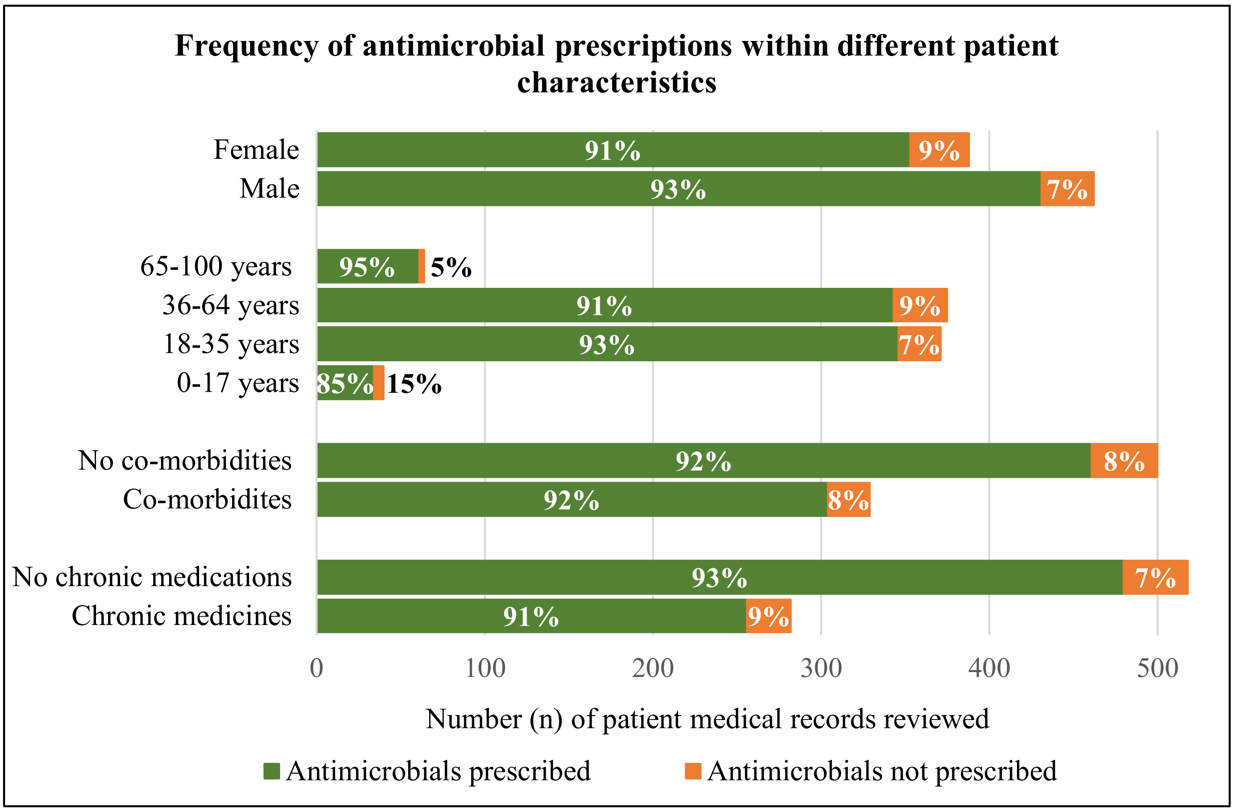

Figure 6: Bar graphs of the frequencies of antimicrobial prescriptions according to the different patient demographics.

- Allergies were not recorded in 13.6% of patient medical records from the ED visits and antimicrobials were still prescribed in 93.1% of these cases. Of these antimicrobials, 89% were penicillin.
- Antimicrobials were mostly prescribed in patients within the normal temperature range of 36.0°C to 37.9°C (86.7%).
- All patients within standard ranges of CRP of ≤ 4 mg/L and 97.5% of WCC within standard ranges of 4.0 to 10.8 x 10^9/L received antimicrobials.
- Only 41 physicians prescribed antimicrobials and sent specimens for microscopy, microbiological culturing and susceptibility testing. This was only 5.2% of patients who had antimicrobials prescribed.
- Commonly identified condition groups and diagnoses that were prescribed antimicrobials is displayed in Figure 7. All urinary tract, dental and oral, cardiovascular and central nervous system conditions received antimicrobials. Patients with animal bites were less likely to receive antimicrobials compared to those without. Patients with UTIs and CAP were more likely to receive antimicrobials compared to those without.
- Majority of patients only received one antimicrobial (57.7%) and the rest receiving receiving two or more antimicrobials.

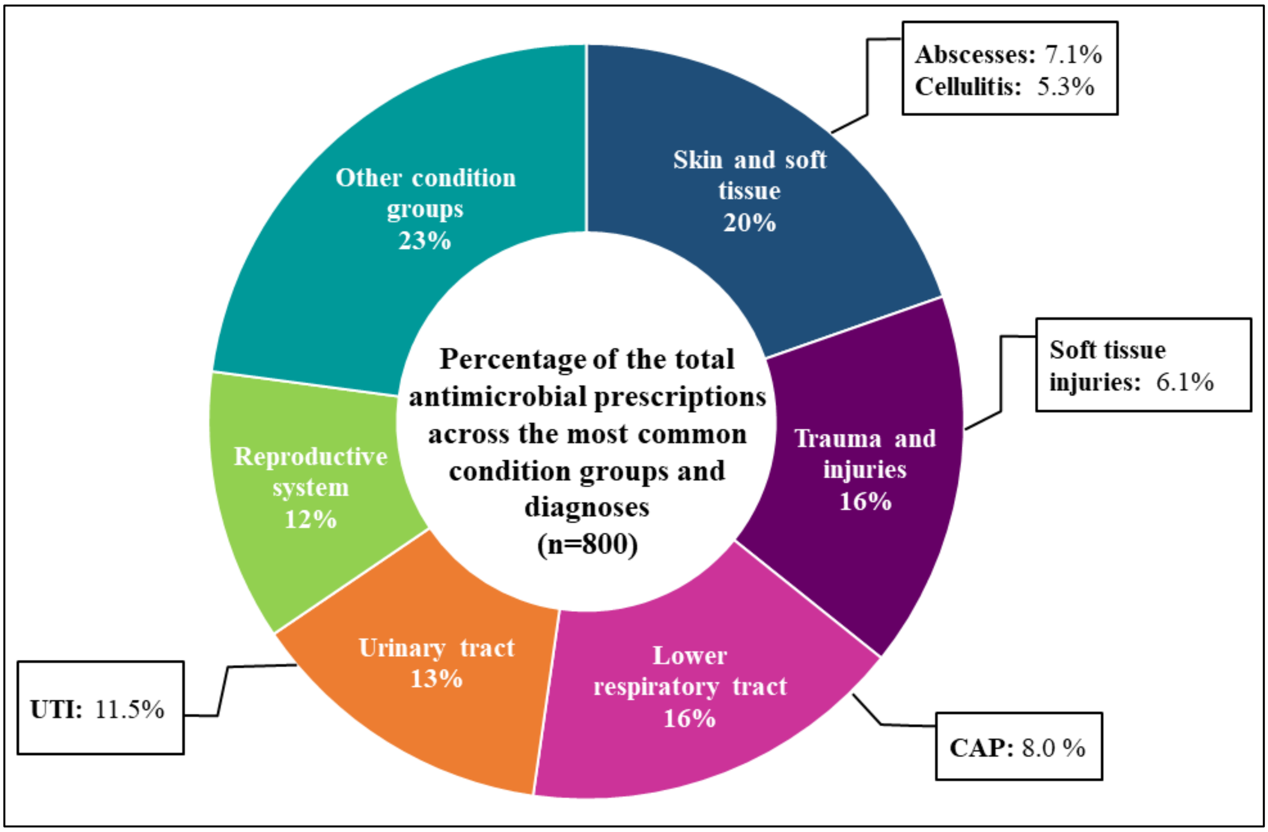

Figure 7: Pie chart showing the percentages of antimicrobial prescriptions as per the most common condition groups and diagnoses.

- The most prescribed group of antimicrobials were antibacterials (96.7%) and penicillin made up 63.4% of these as displayed in Figure 8.
- Sixty different antimicrobial combinations were identified, and the most common combination recorded was amoxicillin/clavulanic acid with azithromycin, followed by amoxicillin/clavulanic acid with metronidazole, and ceftriaxone, azithromycin with metronidazole.

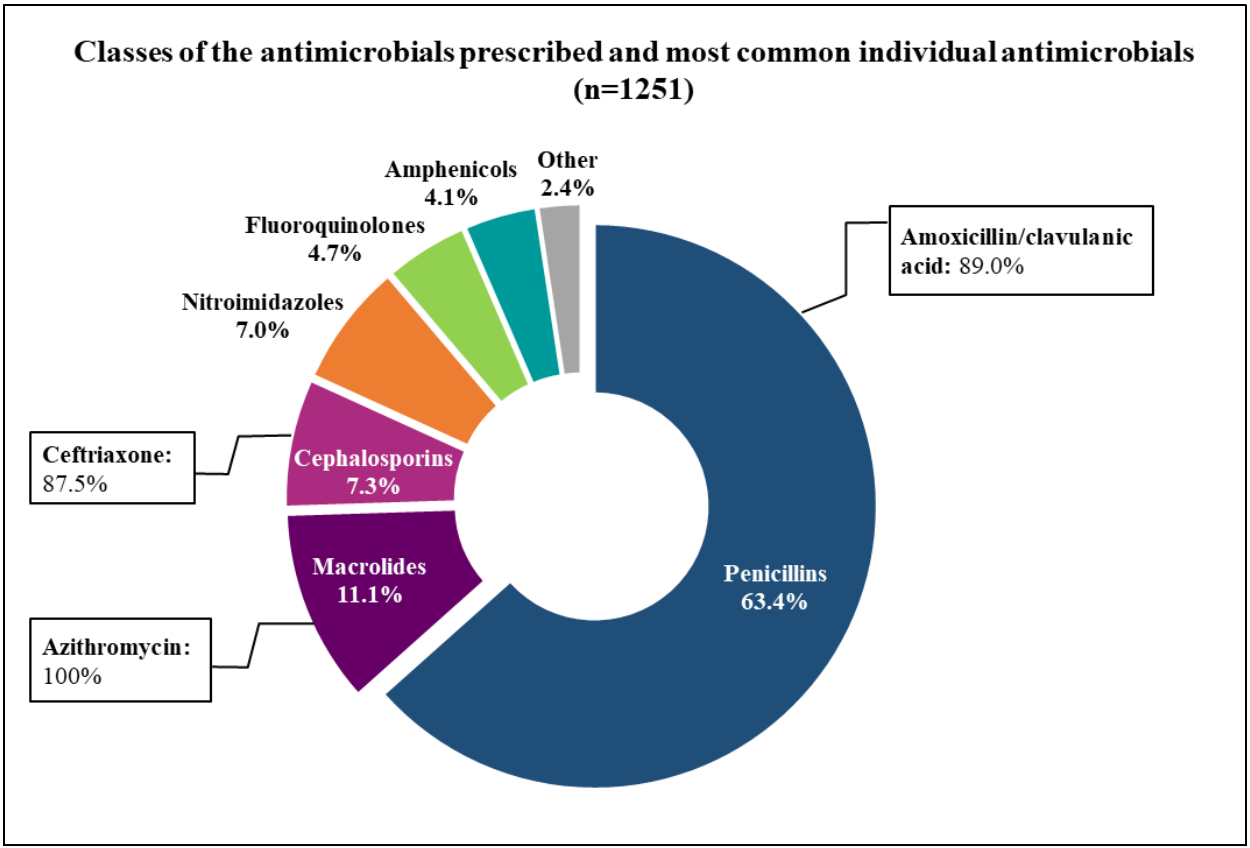

Figure 8: Pie chart showing the frequencies of the different classes of and individual antimicrobials prescribed.

4.4.2 Objective 2: To determine the appropriateness of antimicrobials prescribed per prescription in accordance with STG, SAASP and SAMF

- Summary of the MAI tool analysis per each guideline is displayed in Figure 9.
- The poor appropriateness of antimicrobial prescriptions was noteworthy in the categories of choice, treatment duration, duplication of antimicrobial activity and cost-effectiveness across all three guidelines.

- The most common reason for an inappropriate antimicrobial indication observed across all three guidelines was when an antimicrobial was indicated based on the patient's diagnosis but was not prescribed.

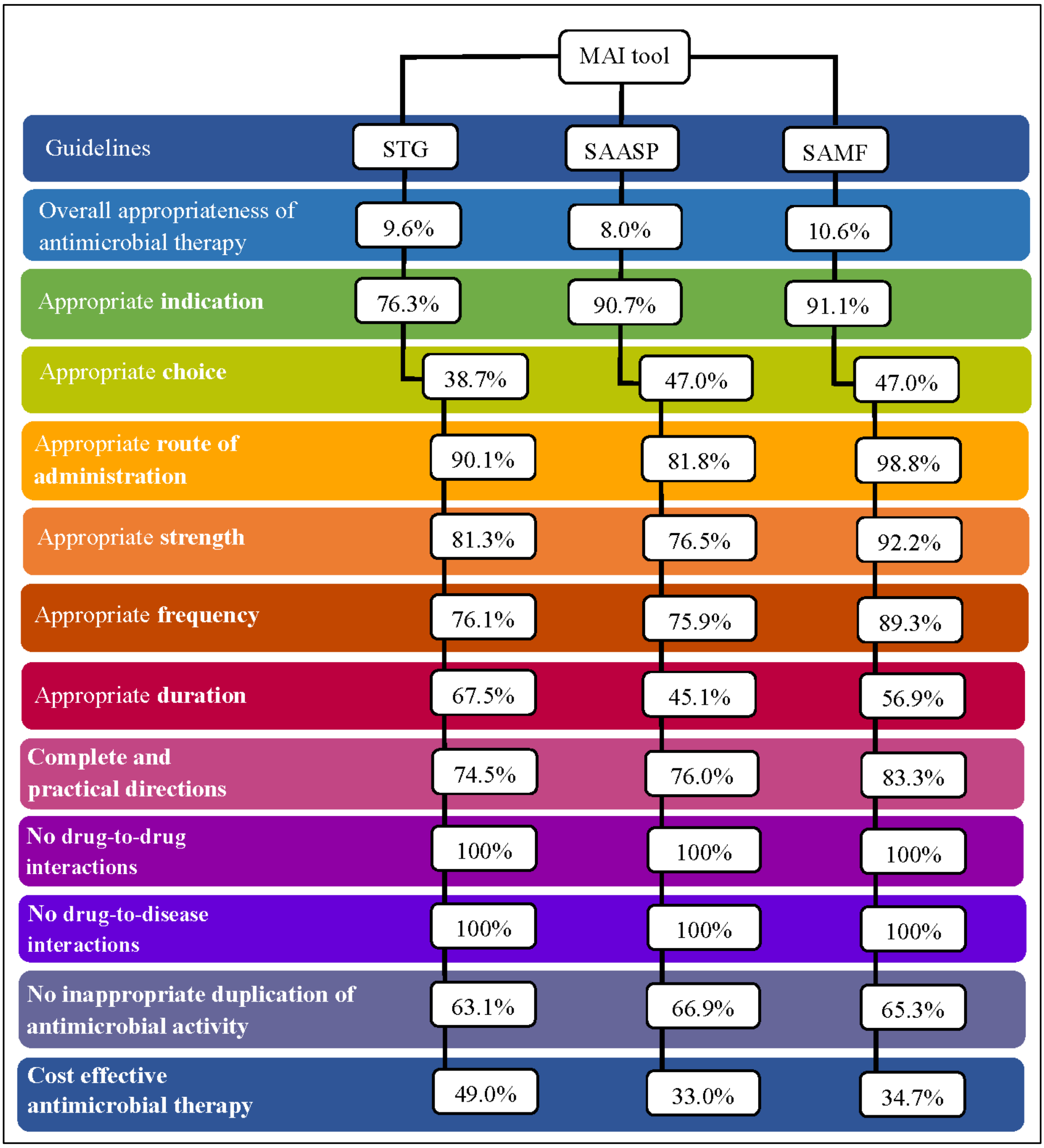

Figure 9: Breakdown of the MAI tool scoring percentages according to the individual guidelines.

4.4.2.1 Key factors contributing to inappropriate antimicrobial prescribing

- Inappropriate antimicrobial strengths were mostly considered too high according to the STG and SAASP (59.7% and 70.9%) and too low according to the SAMF (69.2%).

- Inappropriately prescribed frequencies were mostly considered too seldom across all three guidelines.
- Treatment durations were mostly considered too short across all guidelines and were labelled as inappropriate.
- The common reason for incomplete and/or impractical directions included the omission of "take 4 hourly missing the midnight dose" when prescribing oral aciclovir.
- All guidelines agreed on the unnecessary duplication of antibiotic activity between amoxicillin/clavulanic acid or amoxicillin and azithromycin for CAP, however, there are international guidelines suggesting amoxicillin/clavulanic acid and macrolide combination in moderately severe CAP.
- Doctors often prescribed ceftriaxone, azithromycin and metronidazole for MUS, potentially due to the unknown medical or sexual history of the patient's partner, even though metronidazole is only indicated if the partner has vaginal discharge syndrome according to the STG and EDL. This, however, led to the inappropriate duplication of antimicrobial activity when VDS was not recorded.
- Over 50% of the antimicrobial prescriptions with at least one appropriate antimicrobial prescribed, were not cost-effective across all three guidelines. This was due to inappropriate choices, more expensive routes of administration, higher strengths, higher frequencies and longer treatment durations.
- A large percentage of skin and soft tissue conditions were inappropriately treated (89.7% to 95.4%).
- Abscesses made up a large portion of the skin and soft tissue diagnoses and was poorly managed as 93% and 94.8% of antimicrobial treatments were inappropriate per STG and EDL and SAASP, respectively.
- Animal bites and soft tissue injures were commonly encountered trauma injuries, but also acquired high rates of inappropriate antimicrobial prescriptions. Antimicrobial prescriptions for soft tissue injuries were 100% inappropriate across all three guidelines and 73.2% for animal bite prescriptions according to the STG and EDL. Soft tissue injuries were mostly prescribed antimicrobials when they were not indicated, whereas animal bites often had antimicrobials omitted when they were indicated.
- Noncompliance of antimicrobial prescriptions for urinary tract conditions for all three guidelines stemmed from an inappropriate selection of antimicrobials, along with inappropriate treatment duration and poor cost-effectiveness.

- Percentage of antimicrobial prescriptions for reproductive system conditions that were inappropriate ranged from 91.5% to 96.3%. This was due to poor cost-effectiveness, unnecessary duplication of antimicrobial activity and inappropriate choice of antimicrobials.
- Main reasons for inappropriate amoxicillin/clavulanic acid prescriptions across all three guidelines was due to inappropriate choice, treatment duration, frequency and incomplete and/or impractical directions.
- Azithromycin was frequently inappropriately selected as drug of choice in combination with amoxicillin/clavulanic acid for CAP.
- Metronidazole was chosen inappropriately for cases such as an additional agent with amoxicillin/clavulanic acid for human bites, soft tissue injuries and MUS.
- Ceftriaxone was frequently selected inappropriately, followed by inappropriately prescribed strengths and routes of administration.
- Ciprofloxacin was frequently prescribed with inappropriate durations and inappropriate prescriptions also stemmed from the incorrect choice of ciprofloxacin.

Chapter 5: Summary discussion and conclusion

The misuse and overuse of antimicrobials has amplified global health risks of AMR, leading to increased deaths and MDR infections, emphasising the need for prudent use due to limited new antimicrobial advancements. Antimicrobial stewardship, introduced in the 1990s, advocates for the meticulous, evidence-informed use of antimicrobials via collaborative healthcare teams, with pharmacists playing a pivotal role, to address mounting resistance and enhance patient health. While inpatient AMS shows positive results, its efficacy in ambulatory care, especially amid widespread antibiotic misuse in EDs, remains under-researched. South Africa faces significant AMR challenges due to high antibiotic usage and disease burden; while the AMR Strategy Framework offers direction and pharmacist-led interventions show inpatient success, gaps in surveillance and outpatient research persist. This study provides understanding of prescribing patterns and appropriateness in this setting and has revealed AMS opportunities, that may potentially improve public health and cost-effectiveness.

This study utilised the MAI to assess prescription appropriateness, modified for this study's purpose, building upon the MAI's established use in prior research. Using this tool, 850 patient records, between 01 August 2020 to 31 July 2021, from the ED were systematically reviewed, focusing on antimicrobial prescriptions, diagnoses, and relevant clinical details, with adherence and appropriateness gauged against the latest published standard treatment guidelines.

This study's first objective was to analyse the prescribing patterns of physicians for antimicrobials in the ED. Firstly, patients' demographics were compared to whether or not antimicrobials were prescribed. From this comparison trends that stood out were that age group 65 to 100 years had the highest number of antimicrobials prescribed and only 86.4% of medical records documented whether the patient suffered from a possible allergy, while 93.1% of these patients were prescribed antimicrobials. The frequency of antimicrobial prescriptions was higher in patients in the 36.0°C to 37.9°C temperature category. Next, the condition categories and diagnoses were compared to whether or not antimicrobials were prescribed. It was observed that skin and soft tissue conditions, lower respiratory tract conditions, trauma and injuries, urinary tract conditions and reproductive system conditions accounted for most of the antimicrobial prescriptions. The diagnoses that counted for the most antimicrobial prescriptions were UTIs, CAP, abscesses, soft tissue injuries and cellulitis. The majority of prescriptions included antimicrobials and over half prescribed only one antimicrobial. The most commonly prescribed antibacterial class was penicillins, and the most common antimicrobial combination was amoxicillin/clavulanic acid and azithromycin. It was revealed through this analysis that there is a high usage of broad-spectrum antibiotics.

This study's second objective was to provide a comprehensive analysis of the appropriateness of antimicrobial prescriptions in an ED, focusing on the overall management and the specific appropriateness of antimicrobial prescriptions. It was revealed that only a low percentage of patients received appropriate management in the ED according to national treatment guidelines. This indicates that there is a drastic need for improvement in antimicrobial prescribing practices. Prescribing physicians frequently made appropriate decisions on whether to prescribe antimicrobials, with appropriateness being highest according to the STG and EDL guidelines. However, antimicrobial choices were predominantly inappropriate across all guidelines, posing a significant risk factor for AMR and highlighting the urgent need for improved physician education. Additionally, while many aspects of prescribing, such as route and strength, were often correct, there are still areas requiring attention like treatment duration, frequency, complete directions and cost-effectiveness of prescriptions. The results also revealed that most conditions were treated inappropriately across all guidelines, with varying categories deemed most appropriately or inappropriately treated depending on the guideline reviewed. Common reasons for inappropriateness include the incorrect choice of antimicrobial, treatment duration, duplication of antimicrobial activity, and poor cost-effectiveness of antimicrobial therapy, pinpointing areas requiring AMS interventions. These findings were compared with international studies, emphasising the concerning discrepancy in adherence rates across different countries and outpatient settings, which underscores the global challenge of ensuring appropriate antimicrobial use. These findings emphasise the need for context-specific strategies for AMS and the importance of addressing the factors contributing to the low overall appropriateness of antimicrobial prescribing in ED settings.

The research findings presented in this dissertation have highlighted possible implications and practical applications for enhancing antimicrobial prescribing practices in EDs in South African hospitals. This study provides insight into antimicrobial prescribing patterns, understanding the most prominently prescribed antimicrobials and for what diagnoses. Understanding these patterns can help identify areas of improvement and target interventions accordingly. This study has demonstrated the suitability and reliability of the modified MAI tool for analysing antimicrobial prescribing appropriateness in South African healthcare setting. This tool also helped to identify variability between the different guidelines such as the variety of diagnoses listed, the first-line antimicrobial choices, treatment durations and dosing frequencies. These variabilities alter the overall appropriateness of antimicrobial prescriptions across the different guidelines, because an antimicrobial prescription would be deemed appropriate according to one guideline, but not the other. This tool can be utilised in future studies to assess appropriateness and guide interventions. The findings suggest the need for targeted interventions to improve antimicrobial prescribing practices in the ED. Potential interventions should include education and training programs for physicians, utilizing audit and feedback mechanisms, and implementing dedicated antibiotic charts to enhance adherence to appropriate prescribing guidelines. Another intervention would be to increase awareness of mobile applications like EMGuidance, which are easily accessible and can assist physicians when uncertainty arises to ensure prescribing antimicrobials according to guidelines. The study highlights the potential impact of AMS interventions in reducing overall antimicrobial prescription rates. This finding is crucial in combating AMR and promoting responsible prescribing practices. This research emphasises the importance of improving compliance with prescribing guidelines in terms of antibiotic choice, dose, administration timing, and duration. These factors contribute to the effectiveness of antimicrobial treatment and help prevent the development of resistance. By implementing such interventions, healthcare providers can contribute to the global efforts to combat AMR and optimize patient care.

5.1 Study strengths

The study stands out due to its considerable sample size and the comprehensive 12-month duration, which allows for an in-depth exploration of antimicrobial prescription practices. It uniquely assesses potential duplication of antimicrobial activity and evaluates the cost-effectiveness of prescribed treatments. Moreover, by leveraging three distinct guidelines to assess the appropriateness of antimicrobial use and assessing interrater-reliability, the study ensures a robust, multi-dimensional analysis of prescribing patterns, thereby enhancing the reliability and relevance of its findings in the context of AMS.

5.2 Study limitations

While this study provides valuable insights into the antimicrobial prescribing patterns and appropriateness in the ED of the selected hospital, there are several limitations identified.

The study was a retrospective chart review and limited in that key notes, symptoms or diagnoses may have been omitted in documentation that could have changed the assessment of the prescription (Grenet et al., 2016; Fahs et al., 2017; Garlock et al., 2019). This may lead to bias and overestimating the rate of inappropriate antimicrobial prescriptions acknowledged in this study (Tagashira et al., 2019; Kiel et al., 2020; García-Moreno et al., 2022). Due to its retrospective design, it could not determine factors that influence appropriate antimicrobial prescribing (Haran et al., 2015; Denny et al., 2019). The study was conducted in a single hospital setting, limiting the generalisability of these findings to other EDs across South Africa (Alanazi et al., 2015; Birdsey et al., 2016; Timbrook et al., 2017; Kiel et al., 2020). It is necessary to examine multiple hospital settings to determine national prescribing patterns and appropriateness of antimicrobial use for constructive suggestions to be made. This form of analysis would assist in determining potential root causes for these errors, making AMS interventions more targeted. This study did not analyse the outcomes of antimicrobial treatment or evaluate patient outcomes extensively. In this study it was assessed whether a patient came back to the ED within 14 days of initial visit, however, it had to be at the same facility. Patients who visited other healthcare facilities for further treatment is unknown. Assessing the outcomes of antimicrobial treatment would have offered valuable insights into the effectiveness and appropriateness of the prescribed medications, enhancing patient safety and care quality (Alanazi et al., 2015; Haran et al., 2015; Fahs et al., 2017; Timbrook et al., 2017). It would allow for the identification of any patterns in treatment failures or successes, contributing to a more targeted and rational use of antimicrobials (Acquisto and May, 2020). Furthermore, understanding patient trajectories post-prescription, including those seeking care at different facilities, would provide a fuller picture of antimicrobial impact, guiding improvements in prescribing practices and potentially reducing the development of AMR (Birdsey et al., 2016; Tagashira et al., 2019). A large portion of the diagnoses were not listed in the guidelines used and this led to these antimicrobial treatments being excluded in the assessment of appropriateness. To prevent this, an infectious disease specialist and microbiologist could be included into the research team to assess clinical judgement in these cases (Alanazi et al., 2015; Timbrook et al., 2017; Gasson et al., 2018; Denny et al., 2019). These members could provide valuable insight into the decision-making by physicians rather than reliance on multiple clinical decision-making tools, allowing for simplified information seeking.

5.3 Future study recommendations

Expanding the study across multiple outpatient settings would not only amplify the diversity of the data, but also enhance the robustness and applicability of the findings to a broader healthcare context. Incorporating detailed patient outcomes and clinical data could provide a richer understanding of the effectiveness and side effects of antimicrobial treatments, thereby enabling a more patient-centric approach to care. Documenting the rationale behind each prescription would allow for a nuanced evaluation of the decision-making process, ensuring that antimicrobial use is justified and tailored to individual patient needs. Longitudinal studies could uncover trends and shifts in antimicrobial prescribing practices over time, offering valuable insights into the dynamics of antibiotic resistance and the tangible benefits of stewardship programs. The research and development of a more suitable clinical decision-making tool may be necessary due to the variabilities between different guidelines. This tool can be inclusive of all relevant information present in these guidelines that would assist physicians in reducing the number of resources needed to refer to. Research into guideline updates may be needed, as evident with the amendments made to the MAI tool, such as more details into antimicrobial strength and frequencies, taking of specimens and concern over differential diagnoses. Finally, forging partnerships with other research bodies and stakeholders could drive the co-creation of innovative, evidence-based interventions aimed at optimising antimicrobial usage, ultimately contributing to improved patient outcomes and public health.

5.4 Conclusion

The escalating challenge of AMR, driven by the misuse and overuse of antimicrobials, underscores the critical need for effective AMS programs. This study, set within the context of South Africa's unique disease burden and antimicrobial usage patterns, examined the appropriateness of antimicrobial prescriptions in a specific ED using the modified MAI. Alarmingly, a significant proportion of prescriptions were deemed inappropriate across all guidelines, revealing a pressing requirement for better physician education and targeted AMS interventions in emergency care settings. While the study offers invaluable insights into prescribing patterns, exposing potential areas for improvement, its limitations highlight the necessity for broader, more comprehensive research in multiple hospital settings, integrating patient outcomes, and more detailed prescribing rationale. As the battle against AMR intensifies, it is imperative that focused and collaborative efforts are made to optimize prescribing practices, with this study serving as a stepping stone toward achieving that objective in South Africa's EDs. Future research should expand on these findings, incorporate multiple care settings, and actively involve diverse stakeholders to create impactful, sustainable solutions.

References

Abahamye, A. (2016) Antibiotic stewardship: Factors influencing the choice and outcomes of antimicrobial therapy in a resource-limited, rural, public hospital in uMkhanyakude District, KwaZulu-Natal, South Africa: Pre-intervention phase., 83: 35–44.

Abbott, K.V., Barton, F.B., Terhorst, L., et al. (2016) Retrospective Studies: A Fresh Look. American Journal of Speech-Language Pathology, 25 (2): 157–163. doi:10.1044/2016_AJSLP-16-0025.

Abubakar, U., Syed Sulaiman, S.A. and Adesiyun, A.G. (2019) Impact of pharmacist-led antibiotic stewardship interventions on compliance with surgical antibiotic prophylaxis in obstetric and gynecologic surgeries in Nigeria Lo, T.S. (ed.). PLOS ONE, 14 (3): e0213395. doi:10.1371/journal.pone.0213395.

Academy of Science of South Africa (2019) Surveillance and Response to Infectious Diseases and Comorbidities: An African and German Perspective. Pretoria, South Africa: Academy of Science of South Africa (ASSAf). doi:10.17159/assaf.2019/0042.

Acquisto, N.M. and May, L. (2020) Collaborative Antimicrobial Stewardship in the Emergency Department. Infectious Disease Clinics of North America, 34 (1): 109–127. doi:10.1016/j.idc.2019.10.004.

Adorka, M., Dikokole, M., Mitonga, K., et al. (2013) Healthcare providers' attitudes and perceptions in infection diagnosis and antibiotic prescribing in public health institutions in Lesotho: A cross sectional survey. African Health Sciences, 13 (2): 344–350. doi:10.4314/ahs.v13i2.21.

Adriaenssens, N., Coenen, S., Tonkin-Crine, S., et al. (2011) European Surveillance of Antimicrobial Consumption (ESAC): disease-specific quality indicators for outpatient antibiotic prescribing. BMJ quality & safety, 20 (9): 764–772. doi:10.1136/bmjqs.2010.049049.

Aguilar, G.R., Swetschinski, L.R., Weaver, N.D., et al. (2023) The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. The Lancet Regional Health - Americas, 25: 100561. doi:10.1016/j.lana.2023.100561.

Akenroye, A.T., Baskin, M.N., Samnaliev, M., et al. (2014) Impact of a Bronchiolitis Guideline on ED Resource Use and Cost: A Segmented Time-Series Analysis. Pediatrics, 133 (1): e227–e234. doi:10.1542/peds.2013-1991.

Akpan, M.R., Isemin, N.U., Udoh, A.E., et al. (2020) Implementation of antimicrobial stewardship programmes in African countries: a systematic literature review. Journal of Global Antimicrobial Resistance, 22: 317–324. doi:10.1016/j.jgar.2020.03.009.

Alabi, M.E. and Essack, S.Y. (2022) Antibiotic prescribing amongst South African general practitioners in private practice: an analysis of a health insurance database. JAC-Antimicrobial Resistance, 4 (5): dlac101. doi:10.1093/jacamr/dlac101.

Alanazi, M., Al-Jeraisy, M. and Salam, M. (2015) Prevalence and predictors of antibiotic prescription errors in an emergency department, Central Saudi Arabia. Drug, Healthcare and Patient Safety, p. 103. doi:10.2147/DHPS.S83770.

Ali, K.B.H., Sekma, A., Messous, S., et al. (2021) Antibiotic Use and Appropriateness in the Treatment of Acute Respiratory Tract Infections in Tunisian Primary Care and Emergency Departments (Barometer Study): a Multicenter Cross-sectional Observational Clinical Study. doi:10.21203/rs.3.rs-1027359/v1.

Allison, J.J., Wall, T.C., Spettell, C.M., et al. (2000) The Art and Science of Chart Review. The Joint Commission Journal on Quality Improvement, 26 (3): 115–136. doi:10.1016/S1070-3241(00)26009-4.

Almansoori, N. and Parag, N. (2021) Antibiotic prescribing patterns in Emergency Department at Regional Hospital in South Africa. African Health Sciences, 21 (4): 1651–61. doi:10.4314/ahs.v21i4.19.

Almulhim, A.S., Aldayyen, A., Yenina, K., et al. (2019) Optimization of antibiotic selection in the emergency department for urine culture follow ups, a retrospective pre-post intervention study: clinical pharmacist efforts. Journal of Pharmaceutical Policy and Practice, 12 (1): 8. doi:10.1186/s40545-019-0168-z.

Al-Omari, A., Al Mutair, A., Alhumaid, S., et al. (2020) The impact of antimicrobial stewardship program implementation at four tertiary private hospitals: results of a five-years pre-post analysis. Antimicrobial Resistance & Infection Control, 9 (1): 95. doi:10.1186/s13756-020-00751-4.

Alothman, A., Algwizani, A., Alsulaiman, M., et al. (2016) Knowledge and Attitude of Physicians toward Prescribing Antibiotics and the Risk of Resistance in Two Reference Hospitals. Infectious Diseases: Research and Treatment, 9: IDRT.S40047. doi:10.4137/IDRT.S40047.

Alsan, M., Kammili, N., Lakshmi, J., et al. (2018) Poverty and Community-Acquired Antimicrobial Resistance with Extended-Spectrum β-Lactamase–Producing Organisms, Hyderabad, India. Emerging Infectious Diseases, 24 (8): 1490–1496. doi:10.3201/eid2408.171030.

American Society of Health-System Pharmacists (2010) ASHP Statement on the Pharmacist's Role in Antimicrobial Stewardship and Infection Prevention and Control. American Journal of Health-System Pharmacy, 67 (7): 575–577. doi:10.2146/sp100001.

Anderson, M., Schulze, K., Cassini, A., et al. (2019) A governance framework for development and assessment of national action plans on antimicrobial resistance. The Lancet. Infectious Diseases, 19 (11): e371–e384. doi:10.1016/S1473-3099(19)30415-3.

Anticona Huaynate, C.F., Pajuelo Travezaño, M.J., Correa, M., et al. (2015) Diagnostics barriers and innovations in rural areas: insights from junior medical doctors on the frontlines of rural care in Peru. BMC Health Services Research, 15 (1): 454. doi:10.1186/s12913-015-1114-7.

Ata, M., Hoque, R., Biswas, R.S.R., et al. (2019) Antibiotics Prescribing Pattern at Outpatient Department of A Tertiary Medical College Hospital. Chattagram Maa-O-Shishu Hospital Medical College Journal, 17 (2): 36–39. doi:10.3329/cmoshmcj.v17i2.39775.

Australian Commission on Safety and Quality in Health Care (2023) Antimicrobial Stewardship in Australian Health Care. Sydney: Australian Commission on Safety and Quality in Health Care. Available at: https://www.safetyandquality.gov.au/sites/default/files/2022-09/ams_book_-_cover_acknowledgements_and_contents_0.pdf.

Awad, A. and Hanna, O. (2019) Potentially inappropriate medication use among geriatric patients in primary care setting: A cross-sectional study using the Beers, STOPP, FORTA and MAI criteria Van Dijk, L. (ed.). PLOS ONE, 14 (6): e0218174. doi:10.1371/journal.pone.0218174.

Baker, S.N., Acquisto, N.M., Ashley, E.D., et al. (2012) Pharmacist-Managed Antimicrobial Stewardship Program for Patients Discharged From the Emergency Department. Journal of Pharmacy Practice, 25 (2): 190–194. doi:10.1177/0897190011420160.

Barlam, T.F., Cosgrove, S.E., Abbo, L.M., et al. (2016) Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 62 (10): e51-77. doi:10.1093/cid/ciw118.

Bassetti, S., Tschudin-Sutter, S., Egli, A., et al. (2022) Optimizing antibiotic therapies to reduce the risk of bacterial resistance. European Journal of Internal Medicine, 99: 7–12. doi:10.1016/j.ejim.2022.01.029.

Belachew, S.A., Hall, L. and Selvey, L.A. (2021) Non-prescription dispensing of antibiotic agents among community drug retail outlets in Sub-Saharan African countries: a systematic review and meta-analysis. Antimicrobial Resistance & Infection Control, 10 (1): 13. doi:10.1186/s13756-020-00880-w.

Ben-Ami, R., Olshtain-Pops, K., Krieger, M., et al. (2012) Antibiotic Exposure as a Risk Factor for Fluconazole-Resistant Candida Bloodstream Infection. Antimicrobial Agents and Chemotherapy, 56 (5): 2518–2523. doi:10.1128/AAC.05947-11.

van den Bergh, D., Messina, A.P., Goff, D.A., et al. (2020) A pharmacist-led prospective antibiotic stewardship intervention improves compliance to community-acquired pneumonia guidelines in 39 public and private hospitals across South Africa. International Journal of Antimicrobial Agents, 56 (6): 106189. doi:10.1016/j.ijantimicag.2020.106189.

Birdsey, M., Edwards, G., Abetz, J., et al. (2016) Bite wounds and antibiotic prescription among patients presenting to an Australian emergency department. International Emergency Nursing, 27: 42–45. doi:10.1016/j.ienj.2015.10.007.

Bishaw, B.M., Tegegne, G.T. and Berha, A.B. (2021) Appropriate Use of Ceftriaxone in Sub-Saharan Africa: A Systematic Review. Infection and Drug Resistance, Volume 14: 3477–3484. doi:10.2147/IDR.S329996.

Bishop, B.M. (2016) Antimicrobial Stewardship in the Emergency Department: Challenges, Opportunities, and a Call to Action for Pharmacists. Journal of Pharmacy Practice, 29 (6): 556–563. doi:10.1177/0897190015585762.

Boclé, H., Lavigne, J.-P., Cellier, N., et al. (2021) Effectiveness of early switching from intravenous to oral antibiotic therapy in Staphylococcus aureus prosthetic bone and joint or orthopedic metalware-associated infections. BMC Musculoskeletal Disorders, 22 (1): 315. doi:10.1186/s12891-021-04191-y.

Bork, J.T., Werzen, A., Davé, R., et al. (2020) Improving Antimicrobial Use in Adult Outpatient Clinics: the New Frontier for Antimicrobial Stewardship Programs. Current Infectious Disease Reports, 22 (5): 13. doi:10.1007/s11908-020-00722-1.

Bosu, W.K. and Ofori-Adjei, D. (2000) An audit of prescribing practices in health care facilities of the Wassa West district of Ghana. West African Journal of Medicine, 19 (4): 298–303.

Boyles, T.H., Naicker, V., Rawoot, N., et al. (2017) Sustained reduction in antibiotic consumption in a South African public sector hospital; Four year outcomes from the Groote Schuur Hospital antibiotic stewardship program. South African Medical Journal, 107 (2): 115. doi:10.7196/SAMJ.2017.v107i2.12067.

Boyles, T.H., Whitelaw, A., Bamford, C., et al. (2013) Antibiotic Stewardship Ward Rounds and a Dedicated Prescription Chart Reduce Antibiotic Consumption and Pharmacy Costs without Affecting Inpatient Mortality or Re-Admission Rates Chaturvedi, V. (ed.). PLoS ONE, 8 (12): e79747. doi:10.1371/journal.pone.0079747.

Brink, A.J., Messina, A.P., Feldman, C., et al. (2016a) Antimicrobial stewardship across 47 South African hospitals: an implementation study. The Lancet Infectious Diseases, 16 (9): 1017–1025. doi:10.1016/S1473-3099(16)30012-3.

Brink, A.J., Messina, A.P., Feldman, C., et al. (2016b) From guidelines to practice: a pharmacist-driven prospective audit and feedback improvement model for perioperative antibiotic prophylaxis in 34 South African hospitals. Journal of Antimicrobial Chemotherapy, p. dkw523. doi:10.1093/jac/dkw523.

Bronkhorst, E., Schellack, N. and Gous, A.G. (2020) Contextualising the Pharmacist Practicing Clinical Pharmacy in South Africa – Do we Practice What we Preach? In Review. doi:10.21203/rs.3.rs-55962/v1.

Bronkhorst, E., Shellack, N., Gous, A.G.S., et al. (2014) The need for pharmaceutical care in an intensive care unit at a teaching hospital in South Africa. Southern African Journal of Critical Care, 30 (2): 41. doi:10.7196/SAJCC.194.

Buising, K.L., Thursky, K.A., Black, J.F., et al. (2008) Improving antibiotic prescribing for adults with community acquired pneumonia: Does a computerised decision support system achieve more than academic detailing alone?--A time series analysis. BMC medical informatics and decision making, 8: 35. doi:10.1186/1472-6947-8-35.

Byarugaba, D.K. (2004) Antimicrobial resistance in developing countries and responsible risk factors. International Journal of Antimicrobial Agents, 24 (2): 105–110. doi:10.1016/j.ijantimicag.2004.02.015.

Canadian Society of Hospital Pharmacists (2014) Antimicrobial Stewardship: Statement on the Role of the Pharmacist. Ottawa, ON: Canadian Society of Hospital Pharmacists.

Cantudo-Cuenca, M.R., Jiménez-Morales, A. and Martínez-de La Plata, J.E. (2022) Pharmacist-led antimicrobial stewardship programme in a small hospital without infectious diseases physicians. Scientific Reports, 12 (1): 9501. doi:10.1038/s41598-022-13246-6.

Center for Disease Dynamics, Economics & Policy (2015) State of the World's Antibiotics, 2015. Washington, D.C. Available at: https://onehealthtrust.org/wp-content/uploads/2015/09/the-state-of-the-worlds-antibiotics-_2015.pdf.

Centers for Disease Control and Prevention (2017) Antibiotic prescribing and use in hospitals and long-term care. Available at: https://www.cdc.gov/antibiotic-use/healthcare/#:~:text=Studies%20demonstrate%20that%20improving%20prescribing,all%20while%20reducing%20healthcare%20costs.

Centers for Disease Control and Prevention (2019a) Antibiotic resistance threats in the United States, 2019. Centers for Disease Control and Prevention (U.S.). (DOI: 10.15620/cdc:82532). doi:10.15620/cdc:82532.

Centers for Disease Control and Prevention (2019b) Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.

Charani, E. and Holmes, A.H. (2013) Antimicrobial stewardship programmes: the need for wider engagement. BMJ Quality & Safety, 22 (11): 885–887. doi:10.1136/bmjqs-2013-002444.

Chatterjee, D., Sen, S., Begum, S., et al. (2015) A questionnaire-based survey to ascertain the views of clinicians regarding rational use of antibiotics in teaching hospitals of Kolkata. Indian Journal of Pharmacology, 47 (1): 105. doi:10.4103/0253-7613.150373.

Chaw, P.S., Höpner, J. and Mikolajczyk, R. (2018) The knowledge, attitude and practice of health practitioners towards antibiotic prescribing and resistance in developing countries—A systematic review. Journal of Clinical Pharmacy and Therapeutics, 43 (5): 606–613. doi:10.1111/jcpt.12730.

Cherny, S.S., Nevo, D., Baraz, A., et al. (2020) Revealing antibiotic cross-resistance patterns in hospitalized patients through Bayesian network modelling. Pharmacology and Therapeutics. doi:10.1101/2020.07.02.20144006.

Chetty, D. and Leigh-de Rapper, S. (2023) Exploring the discord between pharmacy education and practice in antimicrobial stewardship. Health SA Gesondheid, 28. doi:10.4102/hsag.v28i0.2114.

Chetty, S. (2021) South Africa’s capacity to conduct antimicrobial stewardship. Southern African Journal of Infectious Diseases, 36 (1). doi:10.4102/sajid.v36i1.297.

Chetty, S., Reddy, M., Ramsamy, Y., et al. (2019) Antimicrobial stewardship in South Africa: a scoping review of the published literature. JAC-Antimicrobial Resistance, 1 (3): dlz060. doi:10.1093/jacamr/dlz060.

Chetty, S., Reddy, M., Ramsamy, Y., et al. (2022) Antimicrobial Stewardship in Public-Sector Hospitals in KwaZulu-Natal, South Africa. Antibiotics, 11 (7): 881. doi:10.3390/antibiotics11070881.

Chibabhai, V. (2022) Incidence of candidemia and prevalence of azole-resistant candidemia at a tertiary South African hospital – A retrospective laboratory analysis 2016–2020. Southern African Journal of Infectious Diseases, 37 (1). doi:10.4102/sajid.v37i1.326.

Clemence, M.C.S., Henderson, A., Greenbury, C.B., et al. (2018) A survey of the antibiotic prescribing practices of doctors in an Australian Emergency Department. Infection, Disease & Health, 23 (2): 67–73. doi:10.1016/j.idh.2017.12.001.

Coccolini, F., Sartelli, M., Sawyer, R., et al. (2024) Antibiotic prophylaxis in trauma: Global Alliance for Infection in Surgery, Surgical Infection Society Europe, World Surgical Infection Society, American Association for the Surgery of Trauma, and World Society of Emergency Surgery guidelines. Journal of Trauma and Acute Care Surgery, 96 (4): 674–682. doi:10.1097/TA.0000000000004233.

Connelly, L.M. (2008) Pilot studies. Medsurg Nursing: Official Journal of the Academy of Medical-Surgical Nurses, 17 (6): 411–412.

Cox, J.A., Vlieghe, E., Mendelson, M., et al. (2017) Antibiotic stewardship in low- and middle-income countries: the same but different? Clinical Microbiology and Infection, 23 (11): 812–818. doi:10.1016/j.cmi.2017.07.010.

Crichton, H., O'Connell, N., Rabie, H., et al. (2018) Neonatal and paediatric bloodstream infections: Pathogens, antimicrobial resistance patterns and prescribing practice at Khayelitsha District Hospital, Cape Town, South Africa. South African Medical Journal, 108 (2): 99. doi:10.7196/SAMJ.2018.v108i2.12601.

Czepiel, J., Dróżdż, M., Pituch, H., et al. (2019) Clostridium difficile infection: review. European Journal of Clinical Microbiology & Infectious Diseases, 38 (7): 1211–1221. doi:10.1007/s10096-019-03539-6.

Dadgostar, P. (2019) Antimicrobial Resistance: Implications and Costs. Infection and Drug Resistance, Volume 12: 3903–3910. doi:10.2147/IDR.S234610.

Dadzie, J.E. and Kanagasabai, U. (2022) A Policy Analysis of the Primary Health Care Approach in Liberia. Hygiene, 2 (1): 44–62. doi:10.3390/hygiene2010004.

Davey, P., Marwick, C.A., Scott, C.L., et al. (2017) Interventions to improve antibiotic prescribing practices for hospital inpatients Cochrane Effective Practice and Organisation of Care Group (ed.). Cochrane Database of Systematic Reviews, 2017 (2). doi:10.1002/14651858.CD003543.pub4.

Dawson-Hahn, E.E., Mickan, S., Onakpoya, I., et al. (2017) Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. Family Practice, 34 (5): 511–519. doi:10.1093/fampra/cmx037.

Day, C., Mendelson, M., Peter, J., et al. (2022) Low self-reported penicillin allergy in South Africa—implications for global public health response. JAC-Antimicrobial Resistance, 5 (1): dlad015. doi:10.1093/jacamr/dlad015.

Dellit, T.H., Owens, R.C., McGowan, J.E., et al. (2007) Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 44 (2): 159–177. doi:10.1086/510393.

Denny, K.J., Gartside, J.G., Alcorn, K., et al. (2019) Appropriateness of antibiotic prescribing in the Emergency Department. Journal of Antimicrobial Chemotherapy, 74 (2): 515–520. doi:10.1093/jac/dky447.

Departments of Health and Agriculture, Forestry and Fisheries (2018) South African Antimicrobial Resistance National Strategy Framework 2018 – 2024. Available at: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/nap-library/south-africa-antimicrobial-resistance-national-action-plan-2018---2024.pdf?sfvrsn=533118b0_1.

Dinh, A., Duran, C., Davido, B., et al. (2017) Impact of an antimicrobial stewardship programme to optimize antimicrobial use for outpatients at an emergency department. Journal of Hospital Infection, 97 (3): 288–293. doi:10.1016/j.jhin.2017.07.005.

Dixon, J. and Duncan, C.J. (2014) Importance of antimicrobial stewardship to the English National Health Service. Infection and Drug Resistance, 7: 145–152. doi:10.2147/IDR.S39185.

Donnelly, J.P., Baddley, J.W. and Wang, H.E. (2014) Antibiotic Utilization for Acute Respiratory Tract Infections in U.S. Emergency Departments. Antimicrobial Agents and Chemotherapy, 58 (3): 1451–1457. doi:10.1128/AAC.02039-13.

Dooling, K., Kandeel, A., Hicks, L., et al. (2014) Understanding Antibiotic Use in Minya District, Egypt: Physician and Pharmacist Prescribing and the Factors Influencing Their Practices. Antibiotics, 3 (2): 233–243. doi:10.3390/antibiotics3020233.

Dougherty, L. and Lamb, J. (eds.) (2008) "Local and Systemic Complications of Intravenous Therapy." In Intravenous therapy in nursing practice. 2nd ed. Oxford, UK Malden, MA: Blackwell Pub. pp. 167–196. Available at: http://ndl.ethernet.edu.et/bitstream/123456789/54338/1/124.pdf#page=181.

Dumkow, L.E. (2024) More than One and Done: the Continued Challenge of Identifying Sustainable Outpatient Antimicrobial Stewardship Strategies. Clinical Infectious Diseases, p. ciad755. doi:10.1093/cid/ciad755.

Dumkow, L.E., Axford, K.L., Suda, K.J., et al. (2018) Impact of a stewardship-focused culture follow-up initiative on the treatment of pharyngitis in the emergency department and urgent care settings. Diagnostic Microbiology and Infectious Disease, 92 (2): 136–142. doi:10.1016/j.diagmicrobio.2018.05.014.

Dumkow, L.E., Beuschel, T.S. and Brandt, K.L. (2017) Expanding Antimicrobial Stewardship to Urgent Care Centers Through a Pharmacist-Led Culture Follow-up Program. Infectious Diseases and Therapy, 6 (3): 453–459. doi:10.1007/s40121-017-0168-8.

Durkin, M.J., Keller, M., Butler, A.M., et al. (2018) An Assessment of Inappropriate Antibiotic Use and Guideline Adherence for Uncomplicated Urinary Tract Infections. Open Forum Infectious Diseases, 5 (9): ofy198. doi:10.1093/ofid/ofy198.

Dyar, O.J., Huttner, B., Schouten, J., et al. (2017a) What is antimicrobial stewardship? Clinical Microbiology and Infection, 23 (11): 793–798. doi:10.1016/j.cmi.2017.08.026.

Dyar, O.J., Tebano, G. and Pulcini, C. (2017b) Managing responsible antimicrobial use: perspectives across the healthcare system. Clinical Microbiology and Infection, 23 (7): 441–447. doi:10.1016/j.cmi.2017.04.016.

Ebied, A.M. and Antonelli, P. (2022) Optimization of Antibiotic Selection in the Emergency Department for Adult Skin and Soft Tissue Infections. Hospital Pharmacy, 57 (1): 83–87. doi:10.1177/0018578720985425.

EMG Technologies Proprietary Limited (2022) EMGuidance. Available at: https://emguidance.com.

Engler, D., Meyer, J. and Schellack, N. (2020) Current antimicrobial stewardship programmes in public sector facilities across South Africa: Has the National AMR Strategy Framework made an impact? International Journal of Infectious Diseases, 101: 94. doi:10.1016/j.ijid.2020.09.269.

Engler, D., Meyer, J.C., Schellack, N., et al. (2021a) Antimicrobial Stewardship Activities in Public Healthcare Facilities in South Africa: A Baseline for Future Direction. Antibiotics, 10 (8): 996. doi:10.3390/antibiotics10080996.

Engler, D., Meyer, J.C., Schellack, N., et al. (2021b) Compliance with South Africa's Antimicrobial Resistance National Strategy Framework: are we there yet? Journal of Chemotherapy, 33 (1): 21–31. doi:10.1080/1120009X.2020.1789389.

Eric, B. and Serges, K. (2019) Evaluation of Antibiotic Prescription in Medical Emergencies of the University Hospital Centre of Cocody-Abidjan. Pharmacology & Pharmacy, 10 (12): 507–518. doi:10.4236/pp.2019.1012042.

Essack, S., Schellack, N., Pople, T., et al. (2011) Part III. GARP: Antibiotic supply chain and management in human health. South African Medical Journal, 101 (8). Available at: http://www.samj.org.za/index.php/samj/article/view/5061.

Eudy, J.L., Pallotta, A.M., Neuner, E.A., et al. (2020) Antimicrobial Stewardship Practice in the Ambulatory Setting From a National Cohort. Open Forum Infectious Diseases, 7 (11): ofaa513. doi:10.1093/ofid/ofaa513.

European Centre for Disease Prevention and Control. (2017) Proposals for EU guidelines on the prudent use of antimicrobials in humans. LU: Publications Office. Available at: https://data.europa.eu/doi/10.2900/9621 (Downloaded: 1 February 2023).

European Centre for Disease Prevention and Control and World Health Organization (2022) Antimicrobial resistance surveillance in Europe 2022: 2020 data. LU: Publications Office. Available at: https://data.europa.eu/doi/10.2900/112339 (Downloaded: 24 April 2024).

Eyler, R.F. and Shvets, K. (2019) Clinical Pharmacology of Antibiotics. Clinical Journal of the American Society of Nephrology, 14 (7): 1080–1090. doi:10.2215/CJN.08140718.

Fahs, I., Shrayteh, Z., Abdulkhalek, R., et al. (2017) Professional practice evaluation of emergency department prescriptions for community-acquired infections in Lebanon. International Journal of Infectious Diseases, 64: 74–79. doi:10.1016/j.ijid.2017.09.010.

Fay, L.N., Wolf, L.M., Brandt, K.L., et al. (2019) Pharmacist-led antimicrobial stewardship program in an urgent care setting. American Journal of Health-System Pharmacy, 76 (3): 175–181. doi:10.1093/ajhp/zxy023.

Feroche, A.T. and Alemu, B.M. (2021) Drug Use Evaluation of Ciprofloxacin at Inpatient and Outpatient Departments of Hiwot Fana Specialized University Hospital, Harar General Hospital and Jagol Hospital in Harar City., 10 (1). Available at: https://www.walshmedicalmedia.com/open-access/drug-use-evaluation-of-ciprofloxacin-at-inpatient-and-outpatient-departments-of-hiwot-fana-specialized-university-hospit.pdf.

Ferre-Sanfrancisco, M., Martín, C.G. and Montero, R.G. (2023) Appropriateness of antibiotic prescription at a Pediatric Emergency department., 2 (3): 161–167. Available at: https://seup.org/wp-content/uploads/2024/02/EP2023-23-161_167.pdf.

Fishman, N., Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, et al. (2012) Policy Statement on Antimicrobial Stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infection Control & Hospital Epidemiology, 33 (4): 322–327. doi:10.1086/665010.

Fleming-Dutra, K.E., Hersh, A.L., Shapiro, D.J., et al. (2016) Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA, 315 (17): 1864. doi:10.1001/jama.2016.4151.

Fofana, A.A. and Mehmet, N. (2022) Prevalence and Incidence rate of HIV/AIDS in West Africa. International Journal of Epidemiology and Health Sciences, 3 (1): 1. doi:10.51757/IJEHS.3.1.2022.247746.

Gaibani, P., Gatti, M., Rinaldi, M., et al. (2021) Suboptimal drug exposure leads to selection of different subpopulations of ceftazidime-avibactam-resistant Klebsiella pneumoniae carbapenemase-producing Klebsiella pneumoniae in a critically ill patient. International Journal of Infectious Diseases, 113: 213–217. doi:10.1016/j.ijid.2021.10.028.

Garau, J. and Bassetti, M. (2018) Role of pharmacists in antimicrobial stewardship programmes. International Journal of Clinical Pharmacy, 40 (5): 948–952. doi:10.1007/s11096-018-0675-z.

García-Moreno, F.J., Escobar-Castellanos, M., Marañón, R., et al. (2022) Adecuacy of pediatric antimicrobial prescribing in the Emergency Department at discharge. Anales de Pediatría (English Edition), 96 (3): 179–189. doi:10.1016/j.anpede.2020.11.015.

Garlock, J., Lee, L., Cucci, M., et al. (2019) Suspected gonorrhea and chlamydia: Incidence and utilization of empiric antibiotics in a health system emergency department. The American Journal of Emergency Medicine, 37 (5): 884–889. doi:10.1016/j.ajem.2018.08.015.

Gasson, J., Blockman, M. and Willems, B. (2018) Antibiotic prescribing practice and adherence to guidelines in primary care in the Cape Town Metro District, South Africa. South African Medical Journal, 108 (4): 304. doi:10.7196/SAMJ.2018.v108i4.12564.

Gay, K.J., Hill, C. and Bell, T. (2010) Accuracy of drug-allergy recording in a District General Hospital. International Journal of Pharmacy Practice, 17 (4): 253–255. doi:10.1211/ijpp.17.04.0010.

Gebretekle, G.B., Haile Mariam, D., Abebe Taye, W., et al. (2020) Half of Prescribed Antibiotics Are Not Needed: A Pharmacist-Led Antimicrobial Stewardship Intervention and Clinical Outcomes in a Referral Hospital in Ethiopia. Frontiers in Public Health, 8: 109. doi:10.3389/fpubh.2020.00109.

Gennai, S., Ortiz, S., Boussat, B., et al. (2018) Evaluation of ceftriaxone prescriptions in the emergency department of a university hospital: an urgent need for improvement and alternative therapy. European Journal of Clinical Microbiology & Infectious Diseases, 37 (11): 2063–2068. doi:10.1007/s10096-018-3339-y.

Gerber, J.S., Jackson, M.A., Tamma, P.D., et al. (2021) Policy Statement: Antibiotic Stewardship in Pediatrics. Journal of the Pediatric Infectious Diseases Society, 10 (5): 641–649. doi:10.1093/jpids/piab002.

Gerber, J.S., Prasad, P.A., Fiks, A.G., et al. (2013) Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial. JAMA, 309 (22): 2345. doi:10.1001/jama.2013.6287.

Gilbert, E.H., Lowenstein, S.R., Koziol-McLain, J., et al. (1996) Chart Reviews In Emergency Medicine Research: Where Are The Methods? Annals of Emergency Medicine, 27 (3): 305–308. doi:10.1016/S0196-0644(96)70264-0.

Giruzzi, M.E., Tawwater, J.C. and Grelle, J.L. (2020) Evaluation of Antibiotic Utilization in an Emergency Department After Implementation of an Antimicrobial Stewardship Pharmacist Culture Review Service. Hospital Pharmacy, 55 (4): 261–267. doi:10.1177/0018578719844171.

González-del Castillo, J., Domínguez-Bernal, C., Gutiérrez-Martín, M.C., et al. (2017) Effect of the inadequacy of antibiotic therapy in the Emergency Department on hospital stays. Enfermedades infecciosas y microbiologia clinica (English ed.), 35 (4): 208–213. doi:10.1016/j.eimce.2017.03.004.

Gordon, J.P., Al Taie, A., Miller, R.L., et al. (2023) Quantifying the Economic and Clinical Value of Reducing Antimicrobial Resistance in Gram-negative Pathogens Causing Hospital-Acquired Infections in Australia. Infectious Diseases and Therapy, 12 (7): 1875–1889. doi:10.1007/s40121-023-00835-9.

Govender, N.P. and Reubenson, G. (2018) Initiatives from the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) to tackle infectious diseases in South Africa and the region. Southern African Journal of Infectious Diseases, 33 (2): 3–4. doi:10.4102/sajid.v33i2.1.

Govender, T., Suleman, F. and Perumal-Pillay, V.A. (2021) Evaluating the implementation of the standard treatment guidelines (STGs) and essential medicines list (EML) at a public South African tertiary institution and its associated primary health care (PHC) facilities. Journal of Pharmaceutical Policy and Practice, 14 (1): 105. doi:10.1186/s40545-021-00390-z.

Grenet, J., Davido, B., Bouchand, F., et al. (2016) Evaluating antibiotic therapies prescribed to adult patients in the emergency department. Médecine et Maladies Infectieuses, 46 (4): 207–214. doi:10.1016/j.medmal.2016.04.006.

Guzmán Molina, C., Velasco Rodríguez-Belvís, M., Coroleu Bonet, A., et al. (2014) Antibiotics in Respiratory Tract Infections in Hospital Pediatric Emergency Departments. Archivos de Bronconeumología (English Edition), 50 (9): 375–378. doi:10.1016/j.arbr.2014.06.013.

Hanlon, J.T. and Schmader, K.E. (2013) The Medication Appropriateness Index at 20: Where It Started, Where It Has Been, and Where It May Be Going. Drugs & Aging, 30 (11): 893–900. doi:10.1007/s40266-013-0118-4.

Hanlon, J.T. and Schmader, K.E. (2022) The Medication Appropriateness Index: A Clinimetric Measure. Psychotherapy and Psychosomatics, 91 (2): 78–83. doi:10.1159/000521699.

Hanlon, J.T., Weinberger, M., Samsa, G.P., et al. (1992) A Randomized, Controlled Trial of a Clinical Pharmacist Intervention to Improve Inappropriate Prescribing in Elderly Outpatients With Polypharmacy.

Hanretty, A.M. and Gallagher, J.C. (2018) Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 38 (6): 674–687. doi:10.1002/phar.2118.

Haran, J.P., Wu, G., Bucci, V., et al. (2015) Treatment of bacterial skin infections in ED observation units: factors influencing prescribing practice. The American Journal of Emergency Medicine, 33 (12): 1780–1785. doi:10.1016/j.ajem.2015.08.035.

Harris, P.A., Taylor, R., Minor, B.L., et al. (2019) The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics, 95: 103208. doi:10.1016/j.jbi.2019.103208.

Harris, P.A., Taylor, R., Thielke, R., et al. (2009) Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics, 42 (2): 377–381. doi:10.1016/j.jbi.2008.08.010.

Havers, F.P., Hicks, L.A., Chung, J.R., et al. (2018) Outpatient Antibiotic Prescribing for Acute Respiratory Infections During Influenza Seasons. JAMA Network Open, 1 (2): e180243. doi:10.1001/jamanetworkopen.2018.0243.

van Hecke, O., Butler, C., Mendelson, M., et al. (2019) Introducing new point-of-care tests for common infections in publicly funded clinics in South Africa: a qualitative study with primary care clinicians. BMJ Open, 9 (11): e029260. doi:10.1136/bmjopen-2019-029260.

Hertzog, M.A. (2008) Considerations in determining sample size for pilot studies. Research in Nursing & Health, 31 (2): 180–191. doi:10.1002/nur.20247.

Hess, D.R. (2004) Retrospective Studies and Chart Reviews. RESPIRATORY CARE, 49 (10).

Hlalo, C. (2018) An investigation into antimicrobial prescribing and usage patterns in the Johannesburg Metro District, Gauteng Province. SA Pharmaceutical Journal, 85 (4): 78–80. doi:10.10520/EJC-10e25132b5.

Hoffman, N., Naicker, H., Botha, A., et al. (2017) Evaluating the use of nystatin oral drops in a paediatric tertiary hospital in South Africa: A Medicine Use Evaluation., 84 (5): 66–68.

Holmes, A.H., Moore, L.S.P., Sundsfjord, A., et al. (2016) Understanding the mechanisms and drivers of antimicrobial resistance. The Lancet, 387 (10014): 176–187. doi:10.1016/S0140-6736(15)00473-0.

Howard, P., Pulcini, C., Levy Hara, G., et al. (2015) An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. Journal of Antimicrobial Chemotherapy, 70 (4): 1245–1255. doi:10.1093/jac/dku497.

Indarwati, F., Mathew, S., Munday, J., et al. (2020) Incidence of peripheral intravenous catheter failure and complications in paediatric patients: Systematic review and meta analysis. International Journal of Nursing Studies, 102: 103488. doi:10.1016/j.ijnurstu.2019.103488.

International Pharmaceutical Federation, (FIP) (2015) Fighting Antimicrobial Resistance: The Contribution of Pharmacists. The Hague: International Pharmaceutical Federation.

Iskandar, K., Murugaiyan, J., Hammoudi Halat, D., et al. (2022) Antibiotic Discovery and Resistance: The Chase and the Race. Antibiotics, 11 (2): 182. doi:10.3390/antibiotics11020182.

Ismail, H., Lowman, W., Govind, C.N., et al. (2019) Surveillance and comparison of antimicrobial susceptibility patterns of ESKAPE organisms isolated from patients with bacteraemia in South Africa, 2016 - 2017. South African Medical Journal, 109 (12): 934. doi:10.7196/SAMJ.2019.v109i12.14079.

Iwu, C.D. and Patrick, S.M. (2021) An insight into the implementation of the global action plan on antimicrobial resistance in the WHO African region: A roadmap for action. International Journal of Antimicrobial Agents, 58 (4): 106411. doi:10.1016/j.ijantimicag.2021.106411.

Jamrozik, E. and Selgelid, M. (eds.) (2020) Ethics and Drug Resistance: Collective Responsibility for Global Public Health. Public Health Ethics Analysis. Cham: Springer International Publishing. doi:10.1007/978-3-030-27874-8.

Joint Commission on Hospital Accreditation (2016) APPROVED: New Antimicrobial Stewardship Standard. Joint Commission Perspectives. Joint Commission on Accreditation of Healthcare Organizations, 36 (7): 1, 3–4, 8.

Junaid, E., Jenkins, L., Swanepoel, H., et al. (2018) Antimicrobial stewardship in a rural regional hospital – growing a positive culture. South African Medical Journal, 108 (7): 546. doi:10.7196/SAMJ.2018.v108i7.13149.

Kabbara, W.K., Meski, M.M., Ramadan, W.H., et al. (2018) Adherence to International Guidelines for the Treatment of Uncomplicated Urinary Tract Infections in Lebanon. Canadian Journal of Infectious Diseases and Medical Microbiology, 2018: 1–6. doi:10.1155/2018/7404095.

Kakkar, A.K., Shafiq, N., Singh, G., et al. (2020) Antimicrobial Stewardship Programs in Resource Constrained Environments: Understanding and Addressing the Need of the Systems. Frontiers in Public Health, 8: 140. doi:10.3389/fpubh.2020.00140.

Kamath, R.S., Sudhakar, D., Gardner, J.G., et al. (2018) Guidelines vs Actual Management of Skin and Soft Tissue Infections in the Emergency Department. Open Forum Infectious Diseases, 5 (1): ofx188. doi:10.1093/ofid/ofx188.

Karakonstantis, S. and Kalemaki, D. (2019) Antimicrobial overuse and misuse in the community in Greece and link to antimicrobial resistance using methicillin-resistant S. aureus as an example. Journal of Infection and Public Health, 12 (4): 460–464. doi:10.1016/j.jiph.2019.03.017.

Kariuki, S., Kering, K., Wairimu, C., et al. (2022) Antimicrobial Resistance Rates and Surveillance in Sub-Saharan Africa: Where Are We Now? Infection and Drug Resistance, Volume 15: 3589–3609. doi:10.2147/IDR.S342753.

Kaufman, A.J., McCready, J. and Powis, J. (2017) Impact of a multifaceted antimicrobial stewardship program: A front-line ownership driven quality improvement project in a large urban emergency department. CJEM, 19 (06): 441–449. doi:10.1017/cem.2017.11.

Kazanjian, P. (2017) "History of antimicrobial stewardship." In LaPlante, K.L., Cunha, C.B., Morrill, H.J., et al. (eds.) Antimicrobial stewardship: principles and practice. 1st ed. UK: CABI. pp. 15–23. doi:10.1079/9781780644394.0015.

Kerr, F., Sefah, I.A., Essah, D.O., et al. (2021) Practical Pharmacist-Led Interventions to Improve Antimicrobial Stewardship in Ghana, Tanzania, Uganda and Zambia. Pharmacy, 9 (3): 124. doi:10.3390/pharmacy9030124.

Kesmodel, U.S. (2018) Cross-sectional studies - what are they good for? Acta Obstetricia et Gynecologica Scandinavica, 97 (4): 388–393. doi:10.1111/aogs.13331.

Keuler, N., Johnson, Y. and Coetzee, R. (2022) Treating urinary tract infections in public sector primary healthcare facilities in Cape Town, South Africa: A pharmaceutical perspective. South African Medical Journal, pp. 487–493. doi:10.7196/SAMJ.2022.v112i7.16258.

Khalil, H., Leversha, A. and Khalil, V. (2011) Drug allergy documentation-time for a change? International Journal of Clinical Pharmacy, 33 (4): 610–613. doi:10.1007/s11096-011-9525-y.

Khan, Y., Kritiotis-Germanis, L., Coetzee, R., et al. (2020) The development of a proposed antimicrobial stewardship curriculum for the South African Bachelor of Pharmacy programme.

Khanina, A., Cairns, K.A., Kong, D.C.M., et al. (2021) The impact of pharmacist-led antifungal stewardship interventions in the hospital setting: a systematic review. Journal of Pharmacy Practice and Research, 51 (2): 90–105. doi:10.1002/jppr.1721.

Kiel, A., Catalano, A., Clark, C.M., et al. (2020) Antibiotic prescribing in the emergency department versus primary care: Implications for stewardship. Journal of the American Pharmacists Association, 60 (6): 789-795.e2. doi:10.1016/j.japh.2020.03.016.

Kilipamwambu, A., Bwire, G.M., Myemba, D.T., et al. (2021) WHO/INRUD core prescribing indicators and antibiotic utilization patterns among primary health care facilities in Ilala district, Tanzania. JAC-Antimicrobial Resistance, 3 (2): dlab049. doi:10.1093/jacamr/dlab049.

King, L.M., Fleming-Dutra, K.E. and Hicks, L.A. (2018) Advances in optimizing the prescription of antibiotics in outpatient settings. BMJ, p. k3047. doi:10.1136/bmj.k3047.

Klein, E.Y., Van Boeckel, T.P., Martinez, E.M., et al. (2018) Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proceedings of the National Academy of Sciences, 115 (15). doi:10.1073/pnas.1717295115.

Kohanski, M.A., DePristo, M.A. and Collins, J.J. (2010) Sublethal Antibiotic Treatment Leads to Multidrug Resistance via Radical-Induced Mutagenesis. Molecular Cell, 37 (3): 311–320. doi:10.1016/j.molcel.2010.01.003.

Krockow, E.M. and Tarrant, C. (2019) The international dimensions of antimicrobial resistance: Contextual factors shape distinct ethical challenges in South Africa, Sri Lanka and the United Kingdom. Bioethics, 33 (7): 756–765. doi:10.1111/bioe.12604.

Kudsk-Iversen, S., Gilbert, J.P. and Azarath, A. (2014) Management of patients presenting with diarrhoea to a regional emergency department in KwaZulu-Natal: Call for clearer, more relevant guidance. Southern African Journal of HIV Medicine, 15 (3): 102–103. doi:10.4102/sajhivmed.v15i3.9.

Labi, A.-K., Obeng-Nkrumah, N., Nartey, E.T., et al. (2018) Antibiotic use in a tertiary healthcare facility in Ghana: a point prevalence survey. Antimicrobial Resistance and Infection Control, 7: 15. doi:10.1186/s13756-018-0299-z.

Lagarde, M. and Blaauw, D. (2023) Levels and determinants of overprescribing of antibiotics in the public and private primary care sectors in South Africa. BMJ Global Health, 8 (7): e012374. doi:10.1136/bmjgh-2023-012374.

Laka, M., Milazzo, A. and Merlin, T. (2021) Inappropriate antibiotic prescribing: understanding clinicians' perceptions to enable changes in prescribing practices. Australian Health Review, 46 (1): 21–27. doi:10.1071/AH21197.

Lalande, J., Vrignaud, B., Navas, D., et al. (2018) A prospective observational study of medication errors in a pediatric emergency department. Archives de Pédiatrie, 25 (6): 355–358. doi:10.1016/j.arcped.2018.06.005.

Laxminarayan, R., Duse, A., Wattal, C., et al. (2013) Antibiotic resistance—the need for global solutions. The Lancet Infectious Diseases, 13 (12): 1057–1098. doi:10.1016/S1473-3099(13)70318-9.

Laxminarayan, R., Van Boeckel, T., Frost, I., et al. (2020) The Lancet Infectious Diseases Commission on antimicrobial resistance: 6 years later. The Lancet Infectious Diseases, 20 (4): e51–e60. doi:10.1016/S1473-3099(20)30003-7.

Le Coz, P., Carlet, J., Roblot, F., et al. (2016) Human resources needed to perform antimicrobial stewardship teams' activities in French hospitals. Médecine et Maladies Infectieuses, 46 (4): 200–206. doi:10.1016/j.medmal.2016.02.007.

Levy-Hara, G., Amabile-Cuevas, C.F., Gould, I., et al. (2011) “Ten commandments” for the appropriate use of antibiotics by the practicing physician in an outpatient setting. Frontiers in Microbiology, 2. doi:10.3389/fmicb.2011.00230.

Li, J., Kang-Birken, S.L., Mathews, S.K., et al. (2019) Role of rapid diagnostics for viral respiratory infections in antibiotic prescribing decision in the emergency department. Infection Control & Hospital Epidemiology, 40 (9): 974–978. doi:10.1017/ice.2019.166.

Lim, K., Olsen, A., Broom, A., et al. (2022) Review of position statements on antimicrobial resistance and stewardship from professional pharmacy organisations. Research in Social and Administrative Pharmacy, 18 (11): 3974–3979. doi:10.1016/j.sapharm.2022.07.001.

Llor, C. and Bjerrum, L. (2016) Antibiotic prescribing for acute bronchitis. Expert Review of Anti-infective Therapy, 14 (7): 633–642. doi:10.1080/14787210.2016.1193435.

Losier, M., Ramsey, T.D., Wilby, K.J., et al. (2017) A Systematic Review of Antimicrobial Stewardship Interventions in the Emergency Department. Annals of Pharmacotherapy, 51 (9): 774–790. doi:10.1177/1060028017709820.

Lowrie, R., Lloyd, S.M., McConnachie, A., et al. (2014) A Cluster Randomised Controlled Trial of a Pharmacist-Led Collaborative Intervention to Improve Statin Prescribing and Attainment of Cholesterol Targets in Primary Care Norata, G.D. (ed.). PLoS ONE, 9 (11): e113370. doi:10.1371/journal.pone.0113370.

Mabila, N., Schellack, N. and Gous, A.G.S. (2016) Antibiotic prescribing patterns among healthcare professionals at Van Velden Memorial Hospital in Tzaneen, Limpopo Province, South Africa. African Journal for Physical Activity and Health Sciences (AJPHES), 22 (1–1): 79–97. doi:10.10520/EJC187403.

Macy, E. and Poon, T.K.-Y. (2009) Self-reported antibiotic allergy incidence and prevalence: age and sex effects. The American Journal of Medicine, 122 (8): 778.e1–7. doi:10.1016/j.amjmed.2009.01.034.

Maddali, N., Cantin, A., Koshy, S., et al. (2021) Antibiotic prescribing patterns for adult urinary tract infections within emergency department and urgent care settings. The American Journal of Emergency Medicine, 45: 464–471. doi:10.1016/j.ajem.2020.09.061.

Magiorakos, A.-P., Srinivasan, A., Carey, R.B., et al. (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical Microbiology and Infection, 18 (3): 268–281. doi:10.1111/j.1469-0691.2011.03570.x.

Magira, E.E., Islam, S. and Niederman, M.S. (2018) Multi-drug resistant organism infections in a medical ICU: Association to clinical features and impact upon outcome. Medicina Intensiva (English Edition), 42 (4): 225–234. doi:10.1016/j.medine.2017.07.003.

Mahmood, R.K., Gillani, S.W., Alzaabi, M.J., et al. (2022) Evaluation of inappropriate antibiotic prescribing and management through pharmacist-led antimicrobial stewardship programmes: a meta-analysis of evidence. European Journal of Hospital Pharmacy, 29 (1): 2–7. doi:10.1136/ejhpharm-2021-002914.

Mahmood, R.K., Gillani, S.W., Saeed, M.W., et al. (2021) Impact of pharmacist-led services on antimicrobial stewardship programs: a meta-analysis on clinical outcomes. Journal of Pharmaceutical Health Services Research, 12 (4): 615–625. doi:10.1093/jphsr/rmab036.

Mahmood, S., Coovadia, A., E Laher, A., et al. (2023) mHealth app usage amongst paediatric department doctors in South Africa. African Health Sciences, 23 (3). doi:10.4314/ahs.v23i3.24.

Majumder, M.A.A., Rahman, S., Cohall, D., et al. (2020) Antimicrobial Stewardship: Fighting Antimicrobial Resistance and Protecting Global Public Health. Infection and Drug Resistance, Volume 13: 4713–4738. doi:10.2147/IDR.S290835.

Makwela, A.B., Grootboom, W.M., Abraham, V., et al. (2023) Antimicrobial Management of Skin and Soft Tissue Infections among Surgical Wards in South Africa: Findings and Implications. Antibiotics, 12 (2): 275. doi:10.3390/antibiotics12020275.

Mamalelala, T.T., Mokone, D.J. and Obeng-Adu, F. (2022) Health-related reasons patients transfer from a clinic or health post to the Emergency Department in a District Hospital in Botswana. African Journal of Emergency Medicine, 12 (4): 339–343. doi:10.1016/j.afjem.2022.07.014.

Manderson, L. (2020) Prescribing, care and resistance: antibiotic use in urban South Africa. Humanities and Social Sciences Communications, 7 (1): 77. doi:10.1057/s41599-020-00564-1.

Manyama, T.L., Tshitake, R.M. and Moloto, N.B. (2020) The role of pharmacists in the renal multidisciplinary team at a tertiary hospital in South Africa: Strategies to increase participation of pharmacists. Health SA = SA Gesondheid, 25: 1357. doi:10.4102/hsag.v25i0.1357.

Maphanga, T.G., Naicker, S.D., Kwenda, S., et al. (2021) In Vitro Antifungal Resistance of Candida auris Isolates from Bloodstream Infections, South Africa. Antimicrobial Agents and Chemotherapy, 65 (9): e00517-21. doi:10.1128/AAC.00517-21.

Marston, B.J., Dokubo, E.K., Van Steelandt, A., et al. (2017) Ebola Response Impact on Public Health Programs, West Africa, 2014–2017. Emerging Infectious Diseases, 23 (13). doi:10.3201/eid2313.170727.

Mashalla, Y., Setlhare, V., Massele, A., et al. (2017) Assessment of prescribing practices at the primary healthcare facilities in Botswana with an emphasis on antibiotics: Findings and implications. International Journal of Clinical Practice, 71 (12): e13042. doi:10.1111/ijcp.13042.

Masich, A.M., Vega, A.D., Callahan, P., et al. (2020) Antimicrobial usage at a large teaching hospital in Lusaka, Zambia Quinn, F. (ed.). PLOS ONE, 15 (2): e0228555. doi:10.1371/journal.pone.0228555.

Matanovic, S.M., Bergman, U., Vukovic, D., et al. (2010) Impact of restricted amoxicillin/clavulanic acid use on Escherichia coli resistance--antibiotic DU90% profiles with bacterial resistance rates: a visual presentation. International Journal of Antimicrobial Agents, 36 (4): 369–373. doi:10.1016/j.ijantimicag.2010.05.019.

Mathibe, L.J. and Zwane, N.P. (2020) Unnecessary antimicrobial prescribing for upper respiratory tract infections in children in Pietermaritzburg, South Africa. African Health Sciences, 20 (3): 1133–1142. doi:10.4314/ahs.v20i3.15.

Matsitse, T.B., Helberg, E., Meyer, J.C., et al. (2017) Compliance with the primary health care treatment guidelines and the essential medicines list in the management of sexually transmitted infections in correctional centres in South Africa: findings and implications. Expert Review of Anti-infective Therapy, 15 (10): 963–972. doi:10.1080/14787210.2017.1382354.

May, L., Cosgrove, S., L'Archeveque, M., et al. (2013) A Call to Action for Antimicrobial Stewardship in the Emergency Department: Approaches and Strategies. Annals of Emergency Medicine, 62 (1): 69-77.e2. doi:10.1016/j.annemergmed.2012.09.002.

May, L., Martín Quirós, A., Ten Oever, J., et al. (2021) Antimicrobial stewardship in the emergency department: characteristics and evidence for effectiveness of interventions. Clinical Microbiology and Infection, 27 (2): 204–209. doi:10.1016/j.cmi.2020.10.028.

McGowan Jr, J.E. and Gerding, D.N. (1996) Does antibiotic restriction prevent resistance? New Horizons (Baltimore, Md.), 4 (3): 370–376.

McHugh, M.L. (2012) Interrater reliability: the kappa statistic. Biochemia Medica, pp. 276–282. doi:10.11613/BM.2012.031.

Mendelson, M., Røttingen, J.-A., Gopinathan, U., et al. (2016) Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. The Lancet, 387 (10014): 188–198. doi:10.1016/S0140-6736(15)00547-4.

Messina, A.P., van den Bergh, D. and Goff, D.A. (2015) Antimicrobial Stewardship with Pharmacist Intervention Improves Timeliness of Antimicrobials Across Thirty-three Hospitals in South Africa. Infectious Diseases and Therapy, 4 (S1): 5–14. doi:10.1007/s40121-015-0082-x.

Mestrovic, T., Robles Aguilar, G., Swetschinski, L.R., et al. (2022) The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. The Lancet Public Health, 7 (11): e897–e913. doi:10.1016/S2468-2667(22)00225-0.

Metlay, J.P., Waterer, G.W., Long, A.C., et al. (2019) Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. American

Journal of Respiratory and Critical Care Medicine, 200 (7): e45–e67. doi:10.1164/rccm.201908-1581ST.

Meyer, J.C., Schellack, N., Stokes, J., et al. (2017) Ongoing Initiatives to Improve the Quality and Efficiency of Medicine Use within the Public Healthcare System in South Africa; A Preliminary Study. Frontiers in Pharmacology, 8: 751. doi:10.3389/fphar.2017.00751.

Michael, C.A., Gillings, M.R., Blaskovich, M.A.T., et al. (2021) The Antimicrobial Resistance Crisis: An Inadvertent, Unfortunate but Nevertheless Informative Experiment in Evolutionary Biology. Frontiers in Ecology and Evolution, 9: 692674. doi:10.3389/fevo.2021.692674.

Mir, S., Brett, D., Adam De La, B., et al. (2019) Antibiotics Overuse and Bacterial Resistance. Annals of Microbiology and Research, 3 (1). doi:10.36959/958/573.

Mistry, R.D., Dayan, P.S. and Kuppermann, N. (2015) The Battle Against Antimicrobial Resistance: Time for the Emergency Department to Join the Fight. JAMA Pediatrics, 169 (5): 421. doi:10.1001/jamapediatrics.2015.79.

Mnge, P., Okeleye, B.I., Vasaikar, S.D., et al. (2017) Species distribution and antifungal susceptibility patterns of Candida isolates from a public tertiary teaching hospital in the Eastern Cape Province, South Africa. Brazilian Journal of Medical and Biological Research, 50 (6): e5797. doi:10.1590/1414-431x20175797.

Mo, S., Thursky, K., Chronas, A., et al. (2023) Metronidazole prescribing practices in Australian hospitals: Measuring guideline compliance and appropriateness to support antimicrobial stewardship. Journal of Infection and Public Health, 16: 90–96. doi:10.1016/j.jiph.2023.10.039.

Mohsen, S., Dickinson, J.A. and Somayaji, R. (2020) Update on the adverse effects of antimicrobial therapies in community practice. Canadian Family Physician Medecin De Famille Canadien, 66 (9): 651–659.

Momanyi, L., Opanga, S., Nyamu, D., et al. (2019) Antibiotic prescribing patterns at a leading referral hospital in Kenya: A point prevalence survey. Journal of Research in Pharmacy Practice, 8 (3): 149. doi:10.4103/jrpp.JRPP_18_68.

Monmaturapoj, T., Scott, J., Smith, P., et al. (2021) Pharmacist-led education-based antimicrobial stewardship interventions and their effect on antimicrobial use in hospital inpatients: a systematic review and narrative synthesis. Journal of Hospital Infection, 115: 93–116. doi:10.1016/j.jhin.2021.06.003.

Morrison, L. and Zembower, T.R. (2020) Antimicrobial Resistance. Gastrointestinal Endoscopy Clinics of North America, 30 (4): 619–635. doi:10.1016/j.giec.2020.06.004.

Moskow, J.M., Cook, N., Champion-Lippmann, C., et al. (2016) Identifying opportunities in EHR to improve the quality of antibiotic allergy data. Journal of the American Medical Informatics Association, 23 (e1): e108–e112. doi:10.1093/jamia/ocv139.

Mthombeni, T.C., Burger, J.R., Lubbe, M.S., et al. (2022) Antibiotic consumption in the public sector of the Limpopo province, South Africa, 2014–2018. Southern African Journal of Infectious Diseases, 37 (1). doi:10.4102/sajid.v37i1.462.

Mueller, K., McCammon, C., Skrupky, L., et al. (2015) Vancomycin Use in Patients Discharged From the Emergency Department: A Retrospective Observational Cohort Study. The Journal of Emergency Medicine, 49 (1): 50–57. doi:10.1016/j.jemermed.2015.01.001.

Müller, B.S., Uhlmann, L., Ihle, P., et al. (2020) Development and internal validation of prognostic models to predict negative health outcomes in older patients with multimorbidity and polypharmacy in general practice. BMJ Open, 10 (10): e039747. doi:10.1136/bmjopen-2020-039747.

Murray, C.J., Ikuta, K.S., Sharara, F., et al. (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 399 (10325): 629–655. doi:10.1016/S0140-6736(21)02724-0.

Natali, K.M. and Nerenberg, S.F. (2021) Evaluating Empiric Therapy for Acute Uncomplicated Cystitis in the Outpatient Setting: A Retrospective Cohort Study. Journal of Emergency Nursing, 47 (5): 789–797. doi:10.1016/j.jen.2021.03.005.

National Department of Health (2013) Antimicrobial Resistance National Strategy Framework 2014 – 2024. Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-

04/Antimicrobial%252520resistance%252520national%252520strategy%252520framework%2525202014-2024.pdf.

National Department of Health (2015) Implementation Plan for the Antimicrobial Resistance Strategy Framework in South Africa: 2014–2019. Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/NDOH%2520AMR%2520Implementation%2520Plan%25202014-2019_0.pdf.

National Department of Health (2017) Guidelines on Implementation of the antimicrobial strategy in South Africa_0.pdf. Pretoria: National Department of Health. Available at: https://www.knowledgehub.org.za/system/files/elibdownloads/2020-03/Guidelines%20on%20Implementation%20of%20the%20antimicrobial%20strategy%20in%20South%20Africa_0.pdf (Downloaded: 1 February 2023).

National Department of Health (2018) Guidelines for the Prevention and Containment of Antimicrobial Resistance in South African Hospitals. Pretoria, South Africa: National Department of Health. Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Guidelines%2520for%2520the%2520prevention%2520and%2520containment%2520of%2520AMR%2520in%2520SA%2520hospitals.pdf.

National Department of Health (2019a) Antimicrobial Resistance - Background Document. National Department of Health. Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Antimicrobial%2520Resistance%2520Background%2520Document.pdf.

National Department of Health (2019b) Essential Drugs Programme. Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List. Fifth. Pretoria, South Africa: The National Department of Health. Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Hospital%2520Level%2520%2528Adult%2529%25202019_v2.0.pdf.

National Department of Health (2020) Essential Drugs Programme. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. Seventh. Pretoria, South Africa: The National Department of Health. Available at: https://www.kznhealth.gov.za/pharmacy/PHC-STG-2020.pdf.

National Department of Health (2022) Surveillance for Antimicrobial Resistance and Consumption of Antimicrobials in South Africa, 2021. Available at: https://knowledgehub.health.gov.za/elibrary/surveillance-antimicrobial-resistance-and-consumption-antimicrobials-south-africa-2021.

National Department of Health, D.C.D., Disabilities and Geriatrics (2014) Management of type 2 Diabetes: At Primary Care Level - January 2014. Pretoria: National Department of Health. Available at: https://www.health.gov.za/wp-content/uploads/2021/09/Management-of-type-2-Diabetes-Electronic-copy-2014_compresseda.pdf (Downloaded: 20 February 2023).

National Institute for Health and Care Excellence, (NICE) (2019) Pneumonia (community-acquired): antimicrobial prescribing. United Kingdom.

Newland, J.G., Gerber, J.S., Weissman, S.J., et al. (2014) Prevalence and Characteristics of Antimicrobial Stewardship Programs at Freestanding Children's Hospitals in the United States. Infection Control & Hospital Epidemiology, 35 (3): 265–271. doi:10.1086/675277.

Nguyen, A.D., Mai-Phan, T.-A., Tran, M.H., et al. (2021) The effect of early switching from intravenous to oral antibiotic therapy: a randomized controlled trial. Journal of Pharmacy & Pharmacognosy Research, 9 (5): 695–703. doi:10.56499/jppres21.1072_9.5.695.

Oberjé, E.J.M., Tanke, M.A.C. and Jeurissen, P.P.T. (2017) Antimicrobial Stewardship Initiatives Throughout Europe: Proven Value for Money. Infectious Disease Reports, 9 (1): 6800. doi:10.4081/idr.2017.6800.

Ofori-Asenso, R. (2016) A closer look at the World Health Organization's prescribing indicators. Journal of Pharmacology and Pharmacotherapeutics, 7 (1): 51–54. doi:10.4103/0976-500X.179352.

Okoro, R.N., Nmeka, C. and Erah, P.O. (2019) Antibiotics prescription pattern and determinants of utilization in the national health insurance scheme at a Tertiary Hospital in Nigeria. African Health Sciences, 19 (3): 2356–2364. doi:10.4314/ahs.v19i3.8.

O'Neill, J. (2014) Antimicrobial resistance: tackling a crisis for the health and wealth of nations. London. Available at: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.

Otaigbe, I.I. and Elikwu, C.J. (2023) Drivers of inappropriate antibiotic use in low- and middle-income countries. JAC-Antimicrobial Resistance, 5 (3): dlad062. doi:10.1093/jacamr/dlad062.

Otieno, P.A., Campbell, S., Maley, S., et al. (2022) A Systematic Review of Pharmacist-Led Antimicrobial Stewardship Programs in Sub-Saharan Africa Zeng, X. (ed.). International Journal of Clinical Practice, 2022: 1–16. doi:10.1155/2022/3639943.

Ouldali, N., Bellêttre, X., Milcent, K., et al. (2017) Impact of Implementing National Guidelines on Antibiotic Prescriptions for Acute Respiratory Tract Infections in Pediatric Emergency Departments: An Interrupted Time Series Analysis. Clinical Infectious Diseases, 65 (9): 1469–1476. doi:10.1093/cid/cix590.

Ourghanlian, C., Lapidus, N., Antignac, M., et al. (2020) Pharmacists' role in antimicrobial stewardship and relationship with antibiotic consumption in hospitals: An observational multicentre study. Journal of Global Antimicrobial Resistance, 20: 131–134. doi:10.1016/j.jgar.2019.07.009.

Paharik, A.E., Schreiber, H.L., Spaulding, C.N., et al. (2017) Narrowing the spectrum: the new frontier of precision antimicrobials. Genome Medicine, 9 (1): 110. doi:10.1186/s13073-017-0504-3.

Palms, D.L., Hicks, L.A., Bartoces, M., et al. (2018) Comparison of Antibiotic Prescribing in Retail Clinics, Urgent Care Centers, Emergency Departments, and Traditional Ambulatory Care Settings in the United States. JAMA Internal Medicine, 178 (9): 1267. doi:10.1001/jamainternmed.2018.1632.

Parente, D.M., Timbrook, T.T., Caffrey, A.R., et al. (2017) Inappropriate prescribing in outpatient healthcare: an evaluation of respiratory infection visits among veterans in teaching versus non-teaching primary care clinics. Antimicrobial Resistance & Infection Control, 6 (1): 33. doi:10.1186/s13756-017-0190-3.

Patel, J., Harant, A., Fernandes, G., et al. (2023) Measuring the global response to antimicrobial resistance, 2020–21: a systematic governance analysis of 114 countries. The Lancet Infectious Diseases, 23 (6): 706–718. doi:10.1016/S1473-3099(22)00796-4.

Patel, M. (2022) Oral Cavity and Candida albicans: Colonisation to the Development of Infection. Pathogens, 11 (3): 335. doi:10.3390/pathogens11030335.

Patel, S.K., Elshaboury, R.H., Gandhi, R.G., et al. (2020) Assessment and Optimization of the Empiric Treatment of Urinary Tract Infections in an Academic Emergency Department Observation Unit. The Journal of Emergency Medicine, 58 (2): 203–210. doi:10.1016/j.jemermed.2019.12.021.

Penesyan, A., Gillings, M. and Paulsen, I. (2015) Antibiotic Discovery: Combatting Bacterial Resistance in Cells and in Biofilm Communities. Molecules, 20 (4): 5286–5298. doi:10.3390/molecules20045286.

Perovic, O., Ismail, H., Van Schalkwyk, E., et al. (2018) Antimicrobial resistance surveillance in the South African private sector report for 2016. Southern African Journal of Infectious Diseases, 33 (4): 114–117. doi:10.1080/23120053.2018.1482646.

Pharmaceutical Group of European Union, (PGEU) (2020) PGEU Best Practice Paper on Antimicrobial Resistance. Brussels, Belgium: Pharmaceutical Group of European Union.

Pierce, J., Apisarnthanarak, A., Schellack, N., et al. (2020) Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries: A position statement for the international society for infectious diseases. International Journal of Infectious Diseases, 96: 621–629. doi:10.1016/j.ijid.2020.05.126.

Pillay, K.K., Ross, A. and Van Der Linde, S. (2012) Trauma unit workload at King Edward VIII Hospital, Durban, KwaZulu-Natal. South African Medical Journal, 102 (5): 307. doi:10.7196/SAMJ.5440.

Poole, N.M., Shapiro, D.J., Fleming-Dutra, K.E., et al. (2019) Antibiotic Prescribing for Children in United States Emergency Departments: 2009–2014. Pediatrics, 143 (2): e20181056. doi:10.1542/peds.2018-1056.

Pourhoseingholi, M.A., Vahedi, M. and Rahimzadeh, M. (2013) Sample size calculation in medical studies. Gastroenterology and Hepatology from Bed to Bench, 6 (1): 14–17.

Prestinaci, F., Pezzotti, P. and Pantosti, A. (2015) Antimicrobial resistance: a global multifaceted phenomenon. Pathogens and Global Health, 109 (7): 309–318. doi:10.1179/2047773215Y.0000000030.

Prusakowski, M.K. and Kuehl, D.R. (2015) Trends in emergency department management of skin abscesses. American Journal of Infection Control, 43 (4): 336–340. doi:10.1016/j.ajic.2015.01.012.

Pulcini, C., Binda, F., Lamkang, A.S., et al. (2019) Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clinical Microbiology and Infection, 25 (1): 20–25. doi:10.1016/j.cmi.2018.03.033.

Pulia, M., Redwood, R. and May, L. (2018) Antimicrobial Stewardship in the Emergency Department. Emergency Medicine Clinics of North America, 36 (4): 853–872. doi:10.1016/j.emc.2018.06.012.

Ramsamy, Y., Steele, G., Parbhoo, N., et al. (2019) Antimicrobial stewardship at Prince Mshiyeni Memorial Hospital in KwaZulu-Natal – a pharmacist's perspective on this multidisciplinary strategy. South African Pharmaceutical Journal, 86 (5).

Raosoft (2004) Raosoft Sample Size Calculator. Available at: http://www.raosoft.com/samplesize.html.

Reddy, K., Ramsamy, Y., Swe Swe-Han, K., et al. (2023) Antimicrobial resistance and antimicrobial stewardship in South Africa: a survey of healthcare workers in academic and nonacademic hospitals. Antimicrobial Stewardship & Healthcare Epidemiology, 3 (1): e202. doi:10.1017/ash.2023.483.

Reygaert, W.C. (2018) An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology, 4 (3): 482–501. doi:10.3934/microbiol.2018.3.482.

Riedl, M.A. and Casillas, A.M. (2003) Adverse drug reactions: types and treatment options. American Family Physician, 68 (9): 1781–1790.

Riordan, M., Ha, K., Sarkar, A., et al. (2017) Abstract 14105: Does Venous Thromboembolism (VTE) Prophylaxis Impact Hospital-Acquired VTE Events for Patients on Dual Antiplatelet Therapy (DAPT). Circulation, 136 (suppl_1): A14105–A14105. doi:10.1161/circ.136.suppl_1.14105.

Rose, J., Crosbie, M. and Stewart, A. (2021) A qualitative literature review exploring the drivers influencing antibiotic over-prescribing by GPs in primary care and recommendations to reduce unnecessary prescribing. Perspectives in Public Health, 141 (1): 19–27. doi:10.1177/1757913919879183.

Rossiter, D., Blockman, M. and Barnes, K.I. (2016) South African medicines formulary. 12th edition. Erasmuskloof, Pretoria: Health and Medical Publishing Group.

Royal Pharmaceutical Society (2017) The pharmacy contribution to antimicrobial stewardship. London: Royal Pharmaceutical Society. Available at: https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Policy/AMS%20policy.pdf.

Ruiz-Ramos, J., Escolà-Vergé, L., Monje-López, Á.E., et al. (2023) The Interventions and Challenges of Antimicrobial Stewardship in the Emergency Department. Antibiotics, 12 (10): 1522. doi:10.3390/antibiotics12101522.

Rwafa-Ponela, T., Goudge, J. and Christofides, N. (2021) Organizational structure and human agency within the South African health system: a qualitative case study of health promotion. Health Policy and Planning, 36 (Supplement_1): i46–i58. doi:10.1093/heapol/czab086.

Salam, Md.A., Al-Amin, Md.Y., Salam, M.T., et al. (2023) Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. Healthcare, 11 (13): 1946. doi:10.3390/healthcare11131946.

Salau, H.D., Orchard, A., Johnston, D., et al. (2023) Antibiotic usage in a South African pediatric medical ward following the introduction of an antibiotic prescription chart. Pan African Medical Journal, 45. doi:10.11604/pamj.2023.45.26.36548.

al Salman, J.M., Alawi, S., Alyusuf, E., et al. (2015) Patterns of antibiotic prescriptions and appropriateness in the emergency room in a major secondary care hospital in Bahrain. The International Arabic Journal of Antimicrobial Agents. doi:10.3823/776.

Sanchez, G.V., Fleming-Dutra, K.E., Roberts, R.M., et al. (2016) Core Elements of Outpatient Antibiotic Stewardship. MMWR. Recommendations and Reports, 65 (6): 1–12. doi:10.15585/mmwr.rr6506a1.

Santiago, R.D., Bazan, J.A., Brown, N.V., et al. (2016) Evaluation of Pharmacist Impact on Culture Review Process for Patients Discharged from the Emergency Department. Hospital Pharmacy, 51 (9): 738–743. doi:10.1310/hpj5109-738.

Sapozhnikov, J., Albarillo, F.S. and Pulia, M.S. (2024) Optimizing Antimicrobial Stewardship in the Emergency Department. Emergency Medicine Clinics of North America, 42 (2): 443–459. doi:10.1016/j.emc.2024.02.003.

Sartelli, M., C. Hardcastle, T., Catena, F., et al. (2020) Antibiotic Use in Low and Middle-Income Countries and the Challenges of Antimicrobial Resistance in Surgery. Antibiotics, 9 (8): 497. doi:10.3390/antibiotics9080497.

Sartorius, B., Gray, A.P., Davis Weaver, N., et al. (2024) The burden of bacterial antimicrobial resistance in the WHO African region in 2019: a cross-country systematic analysis. The Lancet Global Health, 12 (2): e201–e216. doi:10.1016/S2214-109X(23)00539-9.

van Schalkwyk, E., Mpembe, R.S., Thomas, J., et al. (2019) Epidemiologic Shift in Candidemia Driven by Candida auris , South Africa, 2016–2017. Emerging Infectious Diseases, 25 (9): 1698–1707. doi:10.3201/eid2509190040.

Scheepers, L.N., Niesing, C.M. and Bester, P. (2023) Facilitators and barriers to implementing antimicrobial stewardship programs in public South African hospitals. Antimicrobial Stewardship & Healthcare Epidemiology, 3 (1): e34. doi:10.1017/ash.2022.355.

Schellack, N., Benjamin, D., Brink, A., et al. (2017) A situational analysis of current antimicrobial governance, regulation, and utilization in South Africa. International Journal of Infectious Diseases, 64: 100–106. doi:10.1016/j.ijid.2017.09.002.

Schellack, N., Bronkhorst, E., Coetzee, R., et al. (2018) SASOCP position statement on the pharmacist's role in antibiotic stewardship 2018. Southern African Journal of Infectious Diseases, 33 (1): 28–35. doi:10.4102/sajid.v33i1.24.

Schellack, N., Pretorius, R. and Messina, A.P. (2016) 'Esprit de corps': Towards collaborative integration of pharmacists and nurses into antimicrobial stewardship programmes in South Africa. South African Medical Journal, 106 (10): 973. doi:10.7196/SAMJ.2016.v106i10.11468.

Schuurman, N., Cinnamon, J., Walker, B.B., et al. (2015) Intentional injury and violence in Cape Town, South Africa: an epidemiological analysis of trauma admissions data. Global Health Action, 8 (1): 27016. doi:10.3402/gha.v8.27016.

Seigel, T.A., Cocchi, M.N., Salciccioli, J., et al. (2012) Inadequacy of Temperature and White Blood Cell Count in Predicting Bacteremia in Patients with Suspected Infection. The Journal of Emergency Medicine, 42 (3): 254–259. doi:10.1016/j.jemermed.2010.05.038.

Sendi, P., Lora-Tamayo, J., Cortes-Penfield, N.W., et al. (2023) Early switch from intravenous to oral antibiotic treatment in bone and joint infections. Clinical Microbiology and Infection, 29 (9): 1133–1138. doi:10.1016/j.cmi.2023.05.008.

Seni, J., Mapunjo, S.G., Wittenauer, R., et al. (2020) Antimicrobial use across six referral hospitals in Tanzania: a point prevalence survey. BMJ Open, 10 (12): e042819. doi:10.1136/bmjopen-2020-042819.

Shamas, N., Stokle, E., Ashiru-Oredope, D., et al. (2023) Challenges of implementing antimicrobial stewardship tools in Low to Middle Income Countries (LMICs). Infection Prevention in Practice, 5 (4): 100315. doi:10.1016/j.infpip.2023.100315.

Shehab, N., Lovegrove, M.C., Geller, A.I., et al. (2016) US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA, 316 (20): 2115. doi:10.1001/jama.2016.16201.

Shen, L., Wei, X., Yin, J., et al. (2022) Interventions to optimize the use of antibiotics in China: A scoping review of evidence from humans, animals, and the environment from a One Health perspective. One Health, 14: 100388. doi:10.1016/j.onehlt.2022.100388.

Shively, N.R., Buehrle, D.J., Clancy, C.J., et al. (2018) Prevalence of Inappropriate Antibiotic Prescribing in Primary Care Clinics within a Veterans Affairs Health Care System. Antimicrobial Agents and Chemotherapy, 62 (8): e00337-18. doi:10.1128/AAC.00337-18.

Sirijatuphat, R., Choochan, T., Siritongtaworn, P., et al. (2015) Implementation of antibiotic use guidelines for fresh traumatic wound at Siriraj Hospital. Journal of the Medical Association of Thailand = Chotmaihet Thangphaet, 98 (3): 245–252.

Skosana, P., Schellack, N., Godman, B., et al. (2021) A point prevalence survey of antimicrobial utilisation patterns and quality indices amongst hospitals in South Africa; findings and implications. Expert Review of Anti-infective Therapy, 19 (10): 1353–1366. doi:10.1080/14787210.2021.1898946.

Skosana, P.P., Schellack, N., Godman, B., et al. (2022) A national, multicentre, web-based point prevalence survey of antimicrobial use and quality indices among hospitalised paediatric patients across South Africa. Journal of Global Antimicrobial Resistance, 29: 542–550. doi:10.1016/j.jgar.2021.12.003.

Sneddon, J., Afriyie, D., Sefah, I., et al. (2020) Developing a Sustainable Antimicrobial Stewardship (AMS) Programme in Ghana: Replicating the Scottish Triad Model of Information, Education and Quality Improvement. Antibiotics, 9 (10): 636. doi:10.3390/antibiotics9100636.

Solensky, R. (2004) Drug allergy: desensitization and treatment of reactions to antibiotics and aspirin. Clinical Allergy and Immunology, 18: 585–606.

Su, Y.-J. (2014) The value of C-reactive protein in emergency medicine. Journal of Acute Disease, 3 (1): 1–5. doi:10.1016/S2221-6189(14)60001-9.

Suda, K.J., Hicks, L.A., Roberts, R.M., et al. (2013) A national evaluation of antibiotic expenditures by healthcare setting in the United States, 2009. Journal of Antimicrobial Chemotherapy, 68 (3): 715–718. doi:10.1093/jac/dks445.

Suthar, A.B., Vitoria, M.A., Nagata, J.M., et al. (2015) Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. The Lancet HIV, 2 (4): e137–e150. doi:10.1016/S2352-3018(15)00005-3.

Tagashira, Y., Yamane, N., Miyahara, S., et al. (2019) Misuse of Discharge Antimicrobial Prescription in the Emergency Department: An Observational Study at a Tertiary Care Center. Open Forum Infectious Diseases, 6 (2): ofz016. doi:10.1093/ofid/ofz016.

Tarrant, C., Colman, A.M., Jenkins, D.R., et al. (2021) Drivers of Broad-Spectrum Antibiotic Overuse across Diverse Hospital Contexts—A Qualitative Study of Prescribers in the UK, Sri Lanka and South Africa. Antibiotics, 10 (1): 94. doi:10.3390/antibiotics10010094.

Tarrant, C., Krockow, E.M., Nakkawita, W.M.I.D., et al. (2020) Moral and Contextual Dimensions of "Inappropriate" Antibiotic Prescribing in Secondary Care: A Three-Country Interview Study. Frontiers in Sociology, 5: 7. doi:10.3389/fsoc.2020.00007.

Temel, G. and Erdogan, S. (2017) Determining the sample size in agreement studies. Marmara Medical Journal, pp. 101–112. doi:10.5472/marumj.344822.

Thabane, L., Ma, J., Chu, R., et al. (2010) A tutorial on pilot studies: the what, why and how. BMC Medical Research Methodology, 10 (1): 1. doi:10.1186/1471-2288-10-1.

TIBCO Software Inc. (2020) Statistica. Available at: https://www.tibco.com.

Timbrook, T.T., Caffrey, A.R., Ovalle, A., et al. (2017) Assessments of Opportunities to Improve Antibiotic Prescribing in an Emergency Department: A Period Prevalence Survey. Infectious Diseases and Therapy, 6 (4): 497–505. doi:10.1007/s40121-017-0175-9.

Tinker, N.J., Foster, R.A., Webb, B.J., et al. (2021) Interventions to optimize antimicrobial stewardship. Antimicrobial Stewardship & Healthcare Epidemiology, 1 (1): e46. doi:10.1017/ash.2021.210.

Tomas, A. and Aljadeeah, S. (2022) The Overlooked Issue of Outpatient Combination Antibiotic Prescribing in Low- and Middle-Income Countries: An Example from Syria. Antibiotics, 11 (1): 74. doi:10.3390/antibiotics11010074.

Trienski, T.L. and Bhanot, N. (2022) Double Anaerobic Coverage—A Call for Antimicrobial Stewardship. Infectious Diseases in Clinical Practice, 30 (6). doi:10.1097/IPC.0000000000001244.

Trinh, T.D. and Klinker, K.P. (2015) Antimicrobial Stewardship in the Emergency Department. Infectious Diseases and Therapy, 4 (S1): 39–50. doi:10.1007/s40121-015-0084-8.

Umar, L.W., Isah, A., Musa, S., et al. (2018) Prescribing pattern and antibiotic use for hospitalized children in a Northern Nigerian Teaching Hospital. Annals of African Medicine, 17 (1): 26–32. doi:10.4103/aam.aam_44_17.

Van Boeckel, T.P., Gandra, S., Ashok, A., et al. (2014) Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. The Lancet Infectious Diseases, 14 (8): 742–750. doi:10.1016/S1473-3099(14)70780-7.

Van Den Broek, A.K., Van Hest, R.M., Lettinga, K.D., et al. (2020) The appropriateness of antimicrobial use in the outpatient clinics of three hospitals in the Netherlands. Antimicrobial Resistance & Infection Control, 9 (1): 40. doi:10.1186/s13756-020-0689-x.

Van Dijck, C., Vlieghe, E. and Cox, J.A. (2018) Antibiotic stewardship interventions in hospitals in low-and middle-income countries: a systematic review. Bulletin of the World Health Organization, 96 (4): 266–280. doi:10.2471/BLT.17.203448.

Vassar, M. and Holzmann, M. (2013) The retrospective chart review: important methodological considerations. Journal of Educational Evaluation for Health Professions, 10: 12. doi:10.3352/jeehp.2013.10.12.

Venkat, A., Piontkowsky, D.M., Cooney, R.R., et al. (2008) Care of the HIV-Positive Patient in the Emergency Department in the Era of Highly Active Antiretroviral Therapy. Annals of Emergency Medicine, 52 (3): 274–285. doi:10.1016/j.annemergmed.2008.01.324.

Vos, T., Lim, S.S., Abbafati, C., et al. (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396 (10258): 1204–1222. doi:10.1016/S0140-6736(20)30925-9.

Vu, H.T.L., Pham, T.T.T., Duong, Y.H., et al. (2024) Antibiotic prescribing practices of medical doctors in a resource-limited setting and the influence of individual perceptions and stewardship support: a survey in three tertiary hospitals in Vietnam. JAC-Antimicrobial Resistance, 6 (2): dlae064. doi:10.1093/jacamr/dlae064.

Walsh, T.L., Taffe, K., Sacca, N., et al. (2020) Risk Factors for Unnecessary Antibiotic Prescribing for Acute Respiratory Tract Infections in Primary Care. Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 4 (1): 31–39. doi:10.1016/j.mayocpiqo.2019.09.004.

Wang, C., Huttner, B.D., Magrini, N., et al. (2020) Pediatric Antibiotic Prescribing in China According to the 2019 World Health Organization Access, Watch, and Reserve (AWaRe) Antibiotic Categories. The Journal of Pediatrics, 220: 125-131.e5. doi:10.1016/j.jpeds.2020.01.044.

Wang, X. and Cheng, Z. (2020) Cross-Sectional Studies. Chest, 158 (1): S65–S71. doi:10.1016/j.chest.2020.03.012.

Wang, Y., Zhou, C., Liu, C., et al. (2022) The impact of pharmacist-led antimicrobial stewardship program on antibiotic use in a county-level tertiary general hospital in China: A retrospective study using difference-in-differences design. Frontiers in Public Health, 10: 1012690. doi:10.3389/fpubh.2022.1012690.

Wang, Y.-Y., Du, P., Huang, F., et al. (2016) Antimicrobial prescribing patterns in a large tertiary hospital in Shanghai, China. International Journal of Antimicrobial Agents, 48 (6): 666–673. doi:10.1016/j.ijantimicag.2016.09.008.

Wasserman, S., Boyles, T.H. and Mendelson, M. (2014) A Pocket Guide to Antibiotic Prescribing forAdults in South Africa, 2015. Available at: http://www.africanstudies.uct.ac.za/sites/default/files/image_tool/images/55/SAASP%20Antibiotic%20Gudidelines_2015.pdf (Accessed: 16 May 2023).

Wattengel, B.A., DiTursi, S., Schroeck, J.L., et al. (2020) Outpatient antimicrobial stewardship: Targets for urinary tract infections. American Journal of Infection Control, 48 (9): 1009–1012. doi:10.1016/j.ajic.2019.12.018.

Wattengel, B.A., Sellick, J.A., Skelly, M.K., et al. (2019) Outpatient Antimicrobial Stewardship: Targets for Community-acquired Pneumonia. Clinical Therapeutics, 41 (3): 466–476. doi:10.1016/j.clinthera.2019.01.007.

Welch, S. (2015) Antimicrobial stewardship in Australian emergency departments: Antimicrobial Stewardship in Australian EDS. Emergency Medicine Australasia, 27 (5): 427–430. doi:10.1111/1742-6723.12448.

White, A.T., Clark, C.M., Sellick, J.A., et al. (2019) Antibiotic stewardship targets in the outpatient setting. American Journal of Infection Control, 47 (8): 858–863. doi:10.1016/j.ajic.2019.01.027.

Wieters, I., Johnstone, S., Makiala-Mandanda, S., et al. (2024) Reported antibiotic use among patients in the multicenter ANDEMIA infectious diseases surveillance study in sub-saharan Africa. Antimicrobial Resistance & Infection Control, 13 (1): 9. doi:10.1186/s13756-024-01365-w.

de With, K., Allerberger, F., Amann, S., et al. (2016) Strategies to enhance rational use of antibiotics in hospital: a guideline by the German Society for Infectious Diseases. Infection, 44 (3): 395–439. doi:10.1007/s15010-016-0885-z.

World Health Organization (2014) Antimicrobial resistance: global report on surveillance. Geneva: World Health Organization. Available at: https://iris.who.int/handle/10665/112642 (Downloaded: 30 March 2024).

World Health Organization (2015a) Global action plan on antimicrobial resistance. Geneva: World Health Organization. Available at: https://iris.who.int/handle/10665/193736 (Downloaded: 24 April 2024).

World Health Organization (2015b) Global antimicrobial resistance surveillance system: manual for early implementation. Geneva: World Health Organization. Available at: https://iris.who.int/handle/10665/188783 (Downloaded: 24 April 2024).

World Health Organization (2017) The selection and use of essential medicines: report of the WHO Expert Committee, 2017 (including the 20th WHO model list of essential medicines and the 6th model list of essential medicines for children). WHO technical report series;1006. Geneva: World Health Organization. Available at: https://iris.who.int/handle/10665/259481 (Downloaded: 24 April 2024).

World Health Organization (2019a) 2019 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline. Geneva: World Health

Organization. Available at: https://iris.who.int/handle/10665/330420 (Downloaded: 30 March 2024).

World Health Organization (2019b) Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. Geneva: World Health Organization. Available at: https://iris.who.int/handle/10665/329404 (Downloaded: 24 April 2024).

World Health Organization (2021a) Antimicrobial stewardship interventions: a practical guide. Copenhagen: WHO Regional Office for Europe.

World Health Organization (2021b) Global antimicrobial resistance and use surveillance system (GLASS) report 2021. Geneva: World Health Organization. Available at: https://iris.who.int/bitstream/handle/10665/341666/9789240027336-eng.pdf?sequence=1.

World Health Organization (2021c) WHO policy guidance on integrated antimicrobial stewardship activities. Geneva: World Health Organization. Available at: https://iris.who.int/bitstream/handle/10665/341432/9789240025530-eng.pdf?sequence=1https://iris.who.int/bitstream/handle/10665/341432/97892400255 30-eng.pdf?sequence=1.

World Health Organization (2022a) 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization. Available at: https://iris.who.int/bitstream/handle/10665/354545/9789240047655-eng.pdf?sequence=1.

World Health Organization (2022b) Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022. Geneva: World Health Organization. Available at: https://iris.who.int/bitstream/handle/10665/364996/9789240062702-eng.pdf?sequence=1.

Wushouer, H., Wang, Z., Tian, Y., et al. (2020) The impact of physicians’ knowledge on outpatient antibiotic use: Evidence from China’s county hospitals. Medicine, 99 (3): e18852. doi:10.1097/MD.0000000000018852.

Xavier, S.P., Victor, A., Cumaquela, G., et al. (2022) Inappropriate use of antibiotics and its predictors in pediatric patients admitted at the Central Hospital of Nampula, Mozambique. Antimicrobial Resistance & Infection Control, 11 (1): 79. doi:10.1186/s13756-022-01115-w.

Xia, R., Hu, X., Willcox, M., et al. (2019) How far do we still need to go? A survey on knowledge, attitudes, practice related to antimicrobial stewardship regulations among Chinese doctors in 2012 and 2016. BMJ Open, 9 (6): e027687. doi:10.1136/bmjopen-2018-027687.

Xu, J., Huang, J., Yu, Y., et al. (2022) The Impact of a Multifaceted Pharmacist-Led Antimicrobial Stewardship Program on Antibiotic Use: Evidence From a Quasi-Experimental Study in the Department of Vascular and Interventional Radiology in a Chinese Tertiary Hospital. Frontiers in Pharmacology, 13: 832078. doi:10.3389/fphar.2022.832078.

Yadav, K., Meeker, D., Mistry, R.D., et al. (2019) A Multifaceted Intervention Improves Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings Choo, E.K. (ed.). Academic Emergency Medicine, 26 (7): 719–731. doi:10.1111/acem.13690.

Yi, S., Ramachandran, A., Epps, L., et al. (2022) Emergency department antimicrobial use in a low-resource setting: results from a retrospective observational study at a referral hospital in Liberia. BMJ Open, 12 (4): e056709. doi:10.1136/bmjopen-2021-056709.

Yonts, A.B., Kronman, M.P. and Hamdy, R.F. (2018) The Burden and Impact of Antibiotic Prescribing in Ambulatory Pediatrics. Current Problems in Pediatric and Adolescent Health Care, 48 (11): 272–288. doi:10.1016/j.cppeds.2018.09.002.

Zaidi, A.A., Dixon, J., Lupez, K., et al. (2019) The burden of trauma at a district hospital in the Western Cape Province of South Africa. African Journal of Emergency Medicine, 9: S14–S20. doi:10.1016/j.afjem.2019.01.007.

Zatorski, C., Zocchi, M., Cosgrove, S.E., et al. (2016) A single center observational study on emergency department clinician non-adherence to clinical practice guidelines for treatment of uncomplicated urinary tract infections. BMC Infectious Diseases, 16 (1): 638. doi:10.1186/s12879-016-1972-6.

Zeng, L., Hu, D., Choonara, I., et al. (2017) A prospective study of the use of antibiotics in the Emergency Department of a Chinese University Hospital. International Journal of Pharmacy Practice, 25 (1): 89–92. doi:10.1111/ijpp.12335.

Zhang, X., Rowan, N., Pflugeisen, B.M., et al. (2017) Urine culture guided antibiotic interventions: A pharmacist driven antimicrobial stewardship effort in the ED. The American Journal of Emergency Medicine, 35 (4): 594–598. doi:10.1016/j.ajem.2016.12.036.

Appendix A: WITS-HREC (Medical) certificate with approval of amendments

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Ms B Wodrich

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210335

NAME: (Principal Investigator) — Ms B Wodrich

DEPARTMENT: — School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

PROJECT TITLE: — *Antimicrobial stewartship practices in the emergency department of a South African tertiary institution: patterns and appropriateness of antimicrobial prescribing*

Change of study title noted on 2022/08/19

DATE CONSIDERED: — 2021/03/26

DECISION: — Approved unconditionally

CONDITIONS:

NOTE: — If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: — Mesdames S Leigh (nee de Rapper) and Z Booth

APPROVED BY: — Dr CB Penny, ~~Chairperson~~, HREC (Medical)

DATE OF APPROVAL: — 2021/07/26

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 2021-08-03

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2022/02/02

Ms B Wodrich
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

Sent by e-mail to: 1035531@students.wits.ac.za

Dear Ms Wodrich

Re: **Protocol Ref No:** M210335
Protocol Title: *Antimicrobial stewartship practices in the emergency department of a South African tertiary institution: patterns and appropriateness of antibiotic prescribing*
Principal Investigators: Ms B Wodrich

I refer to your e-mail of 2022/01/28.

I confirm that we have noted and approve of your proposal to relocate your study site from the Emergency Department of Charlotte Maxeke Johannesburg Academic Hospital to Helen Joseph Hospital.

Thank you for keeping us informed.

Yours Sincerely

I. Burns

....
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2022/08/19

Ms B Wodrich
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

Sent by e-mail to: 1035531@students.wits.ac.za

Dear Ms Wodrich

Re: **Protocol Ref No:** M210335
Protocol Title: *Antimicrobial stewartship practices in the emergency department of a South African tertiary institution: patterns and appropriateness of antimicrobial prescribing Change of study title noted on 2022/08/19*
Principal Investigators: Ms B Wodrich

Thank you for your letter of 2022/08/01.

I confirm that we have noted and approve of your proposal to change:

1. the patient record data collection period to 2020/08/01 - 2021/07/31
2. the sample size to 850
3. the study title - I attach a modified Clearance Certificate

Thank you for keeping us informed.

Yours Sincerely

I Burns
....
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny
....
Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix B: Helen Joseph Hospital site approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M. Mukansi
Research Committee: Chairperson
Tel :(011) 489-0306/1087
Fax :(011) 489 1038
E mail:Murimisi.mukansi@wits.ac.za

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25 January 2022

To whom it may concern

Subject: HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE APPLICATION

PROTOCOL TITLE: Antimicrobial stewardship practices in the emergency department of a South African Tertiary Institution: Patterns and Appropriateness of antibiotic prescribing.

Principal Investigator: Wodrich Brownwen Anette

Ethics Clearance: Pending

Co- investigator: Wodrich Brownwen Anette

Department: Helen Joseph Hospital

Committee Recommendations

The Committee is giving you Conditional access while awaiting the final ethical clearance certificate from the University of Witwatersrand.

It is the duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Dr. M. Mukansi
Chairperson of HJH Ethic and Research Committee

Appendix C: Protocol assessors meeting feedback and approval of protocol corrections by supervisors

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PROTOCOL ASSESSORS MEETING

Candidate Full Name: . . Bronwen Anette Wodrich . . . .

Student Number: . . 1035531. . . . . Date: . . .14/04/2021 . . . .

School / Department / Division: . .Pharmacy and Pharmacoogy. . . . .
.

1. Type of study *(tick all that apply)***:**

- Quantitative
- Qualitative
- Mixed Methods
- Laboratory
- Clinical
- Other, please specify…**Retrospective chart review**……………………………………..

2. Is title of the study appropriate (*preferably fewer than 20 words*)**?** **Yes** No

Comments:

- Appropriate title

3. Are the study objectives clear and linked to the research aim and title? **Yes** No

Comments:

- Objective 3: Clarify the reason for this objective
- Look at wording of objectives.

4. Is the design of the study appropriate to meet the study objectives? **Yes** No

Comments:

- Will the student be able to extract files based on the symptoms and ICD code? To clarify.
- Use of the pharse investigation. Look at a more suitable word

5. Are the proposed methods and tools appropriate to meet the research objectives? **Yes** No

Comments:

- How will information be deidentified. Make this clearer.
- Data collection tool: As this is a modified tool the student needs to include a pilot study.
- Sample size: re-consider the cut-off age of 65 for the inclusion criteria.

6. **Is the study feasible within the resources of:**

a) The applicant? **Yes** No

b) The department? **Yes** No

c) The time frame? **Yes** No

7. **If this is a PhD protocol assessment: N/A**

a) Is the content original? Yes No

b) Does the content show the scope and depth of a PhD? Yes No

Comments: ______________________________

Do you recommend:

i. Additional revision/amendment of the protocol? Please be specific on the recommendations being made:

- Minor changes needed:
  - Referencing errors.
  - Cut of point for age of patients? Consider making it higher.
  - Please comments in text of the protocol

ii. The appointment of the proposed Supervisor? **Yes** No

Nominee/s:

- Stephanie Leigh (de Rapper)
- Zelna Booth

The appointment of the proposed Co-Supervisor/s and/or additional co-supervisors? Yes No

Nominee/s: ______________________________

iii. Has the Chair of the Assessor Group signed the RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS form? Please attach. **Yes** No

iv. Has the Chair informed the student and supervisor about the Wits ethics requirements, and that if required, they must have either a Wits Human Research Ethics clearance certificate or a Wits Animal Research Ethics clearance certificate? **Yes** No

v. Based on the protocol provided (including any proposed changes by the protocol assessor group), does the student require:

1. Human Research Ethics clearance certificate	**Yes**	No
2. Animal Research Ethics clearance certificate	Yes	No
3. No human or animal ethics certificate is required	Yes	No
4. Unclear, will seek appropriate guidance from the HREC/AREC committees	Yes	No

vi. Has the Postgraduate student and supervisor/s signed the ethics declaration form? **Yes** No

Overall recommendation regarding the protocol:

i. Revision of the protocol to the satisfaction of the Supervisor (**NB: if HoD approval is also required, please specify**): **Yes** No
(***Candidate***: *one copy, list of corrections with page numbers and Supervisor approval letter – submit to PG Office).*

ii. Revision of the protocol to the satisfaction of the Assessor Group/Chair: Yes No
*(**Candidate**: one copy, list of corrections with page numbers, Supervisor approval letter – submit to PG Office and PG Office to forward to the Assessor Group Chair).*

iii. Revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: Yes No
*(**Candidate**: six copies, list of corrections with page numbers, Supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator / for PhD, all six copies to be submitted to the PG Office).*

iv. Candidate goes ahead (*no revision required*): Yes No

<u>Details of Assessors:</u>

Name:	Email:	Sign:
Dr. Tania Rauch-Van der Merwe	tania.vandermerwe@wits.ac.za	
Mrs. Rubina Shaikh	Rubina.shaikh@wits.ac.za	
Dr. Disebo Mabako	Disebo.Maboko@wits.ac.za	

11 March 2019/MP

Details of Assessor Group Chair:

Name:	Email:	Sign:
Dr. Janine van der Linde	Janine.vanderlinde@wits.ac.za	JvdLinde

Date:____14/04/2021________

Department of Pharmacy and Pharmacology
Faculty of Health Sciences I 7 York Road Parktown, 2193 I Johannesburg I South Africa I Tel: +27 11 717 2268

31 May 2021

RE: Approval of protocol corrections by supervisors – Bronwen Wodrich (1035531)

We hereby declare that we approve the corrections made to protocol submission by Ms. Bronwen Wodrich (Student number: 1035531) for the degree of Master in Pharmacy entitled: "Antimicrobial stewardship practices in the emergency department of a South African tertiary institution: Patterns and appropriateness of antibiotic prescribing.

Yours Sincerely,

Ms. Stephanie Leigh-de Rapper

Ms. Zelna Booth

I, the undersigned Head of Department have noted and agreed with all amendments made to the protocol.

Professor Yahya Choonara

Appendix D: Summaries of guidelines and policies developed after WHO GAP

Table 13: Guidelines, policies and reports in different countries developed after the release of the WHO GAP.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
The Core Elements of Outpatient Antibiotic Stewardship ((Centers for Disease Control and Prevention, 2016)	USA	2016	CDC	- Identify opportunities to enhance antibiotic prescribing practices by prioritising key conditions, recognising barriers, and establishing standards for antibiotic use. - Pinpoint potential partners for outpatient antibiotic stewardship initiatives. - Show commitment and accountability for optimising antibiotic prescribing and ensuring patient safety. - Implement at least one policy or practice aimed at improving antibiotic prescribing, evaluate its effectiveness, and adjust as necessary. - Monitor antibiotic prescribing practices and provide regular feedback to clinicians, or encourage clinicians to self-assess their prescribing practices. - Supply educational resources to clinicians and patients on antibiotic prescribing, and ensure access to necessary expertise for optimizing antibiotic use.	- Provide expertise to EDs and emergency medicine clinicians. - Provide advice on over-the-counter medications to alleviate symptoms. - Assist in managing and optimizing medication therapy for patients. - Check for potential drug interactions and patient allergies. - Inform patients about proper antibiotic use and expected side effects. - Provide face-to-face educational training.

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
Implementing an Antibiotic Stewardship Program (Barlam et al., 2016)l	USA	2016	IDSA and SHEA	- **Interventions and Monitoring:** Establish preauthorization and audit/feedback interventions. Implement targeted interventions for specific infectious disease syndromes and conditions. Design strategies to reduce high-risk antibiotics. Use computerized clinical decision support during prescribing. Implement pharmacokinetic monitoring and adjustment for specific antibiotics. Monitor antibiotic use and costs effectively. - **Guidelines and Protocols:** Develop facility-specific guidelines for various patient groups (e.g., neonatal ICU, immunocompromised patients). Promote allergy assessments and penicillin skin testing. Implement guidelines for reducing antibiotic therapy duration. Use stratified antibiograms for better empiric antibiotic therapy guidelines. - **Education and Review:** Encourage routine review of antibiotic regimens. Provide educational resources and support for prescribers. Advocate for rapid diagnostic testing to support appropriate antibiotic use.	- Leader in ASPs - Antibiotic approval in preauthorisation interventions - Provide prospective audit and feedback duties. - Encourage review of appropriateness of antibiotic regimens. - Provide pharmacokinetic input or monitoring. - Provide allergy assessments.

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
				- **Cost and Resistance Management:** Advocate for alternative dosing strategies for cost savings. Implement stewardship strategies in nursing homes and skilled nursing facilities. Address antibiotic use and resistance in specific patient groups (e.g., neonatal ICU, terminally ill patients). - **Technology and Rapid Testing:** Integrate rapid viral and diagnostic testing with ASP support. Use serial PCT measurements in ICUs for better antibiotic management. Incorporate nonculture-based fungal markers for antifungal stewardship	
Proposals for EU guidelines on the prudent use of antimicrobials in humans (European Centre for Disease Prevention and Control., 2017)	European Union	2017	European Centre for Disease Prevention and Control	- **Clinical Guidance:** Develop and maintain national guidelines for infection management. Provide decision support tools for appropriate testing and treatment. Regularly review and update guidelines. - **Regulation:** Ensure access to essential antimicrobials and manage shortages. Limit use of last-resort antimicrobials. Regulate internet sales and prescription practices. Explore special labelling and unit dispensing. - **Stewardship Programs:** - Implement AMS across all healthcare settings.	- **Role and Expertise of Pharmacists:** Gatekeepers of antimicrobial use. Providing advice and information on safe, rational, and effective use of antimicrobials. Importance of appropriate training, guidelines, and information for pharmacists. - **Dispensing and Adherence:** Dispensing antimicrobials only with a prescription or under regulated provisions. Ensuring patient understanding of dosage and duration to improve adherence. Promoting proper disposal of leftover antimicrobials. Notifying adverse events related to antimicrobial use.

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
				Educate and train specialists in infectious diseases and microbiology. Monitor, audit and provide feedback on antimicrobial use. Use electronic prescribing systems linked to diagnostic data. - **Education and Awareness:** Promote continuous professional development in antimicrobial use. Include stewardship training in medical and related curricula. Conduct public awareness campaigns on antimicrobial resistance and proper use. Introduce educational programs in schools on antimicrobial use and hygiene.	- **Antimicrobial Stewardship in Hospitals:** Pharmacists as members of antimicrobial stewardship teams. Involvement in multidisciplinary care for antimicrobial management. Reviewing prescriptions, antimicrobial duration, and advising on restricted antimicrobials. Providing dosage, preparation, and administration advice, especially for special patient groups. Monitoring antimicrobial use. - **Public Health and Education:** Participation in public health campaigns for prudent antimicrobial use. Advising on contraindications, drug interactions, and food-drug interactions to patients and health professionals.
The Core Elements of Human Antibiotic Stewardship Programs in Resource-Limited Settings: National and Hospital Levels (Centers for Disease Control and Prevention, 2018)	USA	2018	CDC	- Promote the establishment of national committees and teams with defined roles, develop antibiotic stewardship action plans at national or sub-national levels, participate in antibiotic awareness campaigns and adopt policies that mandate prescriptions for antibiotics. - Develop and ensure access to recommended formularies, create and promote adherence to evidence-based treatment guidelines for common clinical syndromes, promote diagnostic stewardship and support the inclusion of antibiotic stewardship training in	- Provide ASP leadership and oversee implementation - Member of AMS committee. - Alerts to clinicians where prescriptions may be overlapping or duplicative in antimicrobial activity. - Providing interventions such as prior authorisation for select antibiotics, antibiotic restrictions, automatic stop orders and automatic changes (such as intravenous to oral switch).

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
				pre-service curriculums or stand-alone courses. - Enforce prescription requirements, track antibiotic dispensing and set national improvement targets, measure and assess antibiotic use, describe resistance patterns to enhance treatment guidelines and identify priority pathogens, monitor antibiotic quality and address factors driving inappropriate prescribing behaviour.	
The Core Elements of Hospital Antibiotic Stewardship Programs (Centers for Disease Control and Prevention, 2019)	USA	2019	CDC	- Hospital leadership that is committed and dedicated towards necessary human, financial, and information technology resources. - Accountability of an appointed leader or co-leaders, such as a physician and pharmacist, that are responsible for program management and outcomes. - Pharmacy expertise by an appointed pharmacist, who is also the co-leader of the stewardship program, who helps lead implementation efforts to improve antibiotic use. - Action towards implementing interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use. - Tracking and monitoring antibiotic prescribing, impact of interventions, and other important outcomes.	- **Leadership:** Co-lead stewardship programs. Lead implementation efforts for optimal antibiotic use. - **Interventions:** Conduct prospective audits and feedback. Manage preauthorization processes. Develop and enforce treatment guidelines. Implement pharmacy-based interventions like dose adjustments and automatic intravenous to oral changes. - **Monitoring:** Track antibiotic use and resistance patterns. Monitor adherence to guidelines and interventions. Provide feedback to prescribers and leadership. - **Education:** Educate healthcare providers on optimal antibiotic use and resistance Engage in case-based education and public health campaigns. - **Collaboration:** Work with microbiology labs for diagnostic stewardship. Collaborate with committees to develop and implement policies.

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	- Summary of AMS Standards/Fundamentals	- Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
				- Reporting information, regularly, on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership. - Educating prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.	
Policy Statement: Antibiotic Stewardship in Paediatrics (Gerber et al., 2021)	USA	2021	American Academy of Paediatrics Committee on Infectious Diseases and PIDS	- **Purpose:** Minimize antibiotic overuse to reduce resistance and adverse effects. Optimize clinical outcomes through appropriate antibiotic use. - **Core Components:** Involves paediatric specialists, medical directors and clinical pharmacists. Requires support from leadership and collaboration with various healthcare stakeholders. **Strategies:** Implement clinical guidelines for infections. Use prior approval or post-prescription review to manage antibiotic use. Conduct pharmacy-driven interventions like dose optimisation. - **Monitoring:** Regularly track antibiotic use and resistance patterns. Report findings to healthcare staff and adjust practices as needed. - **Education:** Train healthcare workers on antibiotic resistance and optimal prescribing. Engage nurses in stewardship efforts.	- Core team member of ASP with comprehensive knowledge of the diagnosis and management of paediatric infectious diseases - Carry out routine interventions - Lead activities to compile and validate antibiotic use data - Link and encourage agreements about stewardship and pharmacy goals between providers, department of pharmacy and the therapeutic standards committee.

Table 12: Guidelines, policies and reports in different countries developed after the release of the WHO GAP continued.

Name of Guidelines/Policy	Country	Year of Publication	Founding Institution	Summary of AMS Standards/Fundamentals	- Roles of the clinical pharmacist/pharmacist/ infectious disease pharmacist/ specialist pharmacist
				- **Outpatient Focus:** Standardize antibiotic prescribing guidelines in outpatient settings. Emphasize narrow-spectrum antibiotics and shorter antibiotic therapy durations. - **Challenges:** Adapt interventions to various settings. Address cultural influences on prescribing. Develop effective metrics and involve patient perspectives. - **Recommendations:** Establish robust stewardship programs across paediatric healthcare. Use data-driven interventions and continuous education. Monitor and adjust strategies for effective stewardship and improved patient outcomes.	

Appendix E: Summaries of published literature that assessed or reported on appropriateness of antimicrobial prescriptions in emergency care or outpatient settings

Table 14: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA.

Authors, (year)	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Fleming-Dutra et al., 2016	Cross-sectional surveys: National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), non- federally-employed, office-based physicians primarily engaged in patient care, emergency departments and outpatient departments of non-federal general and short-stay hospitals.	184 032	2 years	- Acute respiratory conditions - Sinusitis - Suppurative otitis media - Pharyngitis	- 12.6% of the total sample had antibiotic prescriptions	- 69.8% of antibiotic prescriptions per 1000 population are estimated to be appropriate annually 37% of children tested positive for group A *Streptococcus*, but 56.2% of visits by children with pharyngitis were associated with antibiotic prescribing 18% of adults have a positive test result for group A *Streptococcus*, but 72.4% of visits by adults were associated with antibiotic prescribing. 50% of antibiotic prescriptions for acute respiratory conditions per 1000 population are estimated to be appropriate annually - 85% of antibiotic prescriptions per 1000 population for other conditions are estimated to be appropriate annually - estimated 30% of outpatient oral antibiotic prescriptions may have been inappropriate
Garlock et al., (2019)	Retrospective cohort study, condition specific, health system consisting of a level 1 trauma tertiary-care hospital-based ED and three free-standing EDs	490	1 year	- Gonorrhoea and/or chlamydia	- Azithromycin and ceftriaxone prescribed in 47% of 278 cases	- 278 patients who were treated empirically, 74% of patients had a negative assay - 87% of patients with a positive assay received empiric treatment - 50% of patients with a negative assay of received empiric treatment

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Haran et al., 2015	Prospective cohort study, condition specific, ED observation unit of an academic medical centre.	193	1 year	- Cellulitis - Abscess	- Vancomycin (39.4%) - First-generation cephalosporins (19.2%) - Clindamycin (18.7%) - Penicillin inhibitor combination antibiotics (8.8%)	- 43% were treated according to IDSA guidelines - 42% were over-treated - 15% were undertreated - Older patients (≥ 50 years old) were 48% more likely to be over-treated than younger patients - Patients with abscesses were more likely to be over-treated - Women were 58% more likely to be undertreated than men - IV use of vancomycin and clindamycin was associated with patients being over-treated
Kamath et al., 2018	Retrospective analysis, condition specific, ED at a large tertiary care hospital	214	Not stated	- SSTI - Non-purulent: cellulitis - Purulent: abscesses and infected wounds	- Trimethoprim/ sulfamethoxazole - Vancomycin - Penicillins - Piperacillin/ tazobactam - Linezolid - Ciprofloxacin - Cefazolin	- According to IDSA guidelines, non-recommended antibiotics were prescribed in 71% of non-purulent infections and 68.4% of purulent infections - Abscesses of mild severity were mostly treated with antibiotics, which according to guidelines could have been managed by incision and drainage alone. - Treatment fully complied with guidelines in 20.1% of cases

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Kiel et al., 2020	Prospective observational cohort study, ED and primary healthcare facilities belonging to healthcare system group	1566 - 488 ED - 1078 primacy care	9 months	In the ED: - Bronchitis - CAP - COPD - Epididymitis - Gastro-intestinal conditions - Otitis media - Pharyngitis - Prostatitis - Sinusitis - UTI - SSTI - STI	In the ED: - Amoxicillin/clavulanic acid (10.7%) - Amoxicillin (3.3%) - Azithromycin (26.4%) - Beta-lactam and trimethoprim/ sulfamethoxazole (5.5%) - Cefdinir/ Cefpodoxime (7%) - Cephalexin (19.3%) - Fluoroquinolones (14.5%) - Trimethoprim/ sulfamethoxazole (10.7%)	In the ED: - 63.1% of antibiotics were correct empiric choices for indication - 88.1% of antibiotics' doses were correct - 86.1% of antibiotics' durations were correct - 73.6% of antibiotics were indicated and prescribed - 43.4% of antibiotic prescriptions were overall appropriate
Maddali et al., 2021	Non-interventional, retrospective chart review, condition specific, ED of a single, urban, academic medical centre and off-site urgent care within a large, academic health system	- ED: 104 - Urgent care: 80	6 months	- Uncomplicated UTI - Complicated UTI - Pyelonephritis	- Ciprofloxacin (17.4%) - Levofloxacin (1.6%) - Nitrofurantoin (35.9%) - Trimethoprim/ sulfamethoxazole (9.2%) - Cefdinir (2.2%) - Cephalexin (20.1%) - Cefpodoxime (13.0%) - Cefuroxime (0.5%)	- Uncomplicated UTI: 64% of patients received appropriate first-line antibiotic therapy with nitrofurantoin - Empiric antibiotic therapy with trimethoprim/sulfamethoxazole and cephalexin for uncomplicated UTIs were also prescribed despite low activity on the institutional antibiogram - Extended antibiotic duration was prescribed in approximately 21% of ED and 46% urgent care patients

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Mueller et al., (2015)	Single-centre, retrospective, observational cohort study, drug-specific, ED of an urban, academic, tertiary care institution	526	18 months	- SSTI - Fever - UTI - Laceration - Altered mental status - Headache - Device complication - Meningitis - Hypotension - Bacteraemia - Osteomyelitis - Pneumonia	- Vancomycin (100%) - Trimethoprim/ sulfamethoxazole (23%) - Ceftriaxone (10%) - Cefepime (7%) - Piperacillin/tazobactam (7%) - Clindamycin (6%) - Cefazolin (4%) - Ciprofloxacin (5%) - Ampicillin/sublactam (5%) - Cephalexin (3%) - Other (8%)	- 9% of vancomycin prescriptions met criteria for use in the setting of suspected MRSA infection according to 2011 ISDA guidelines - After receiving vancomycin 42% of these patients presented to the ED with the same problem within one month, and 12% patients required hospital admission for the same diagnosis within one month - Majority of patients received only 1 (68%) or 2 (27%) doses of vancomycin - Majority of patients received a suboptimal vancomycin dosing strategy (underdosed and one dose only)
Patel et al., 2020	Retrospective, single-centre study, condition specific, in ED observation unit of a large, urban, academic medical centre	150	3 months	- Uncomplicated cystitis - Complicated cystitis - Pyelonephritis	- Amoxicillin (0.66%) - Amoxicillin/clavulanic acid (1.33%) - Ampicillin (0.66%) - Azithromycin (1.33%) - Cefazolin (5.33%) - Cefepime (3.33%) - Cefpodoxime (0.66%) - Ceftriaxone (6.66%) - Cephalexin (0.66%) - Cefoxitin (0.66%) - Ciprofloxacin (2.66%) - Levofloxacin (0.66%)	- 87% of patients with an uncomplicated or complicated cystitis were administered guideline-congruent empiric antibiotic therapy - 57% of patients with pyelonephritis were administered guideline-congruent antibiotic therapy - Of patients with pyelonephritis who received guideline-incongruent treatment were empirically started on oral antibiotics without an initial intravenous dose of ceftriaxone or gentamicin, as per IDSA guidelines - Most treatment durations for antibiotics aligned with best-practice recommendations

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study time period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
					- Nitrofurantoin (0.66%) - Trimethoprim/ sulfamethoxazole (0.66%) - Vancomycin (6.66%)	- 60% of fluoroquinolones were prescribed a longer than recommended duration - 87% of beta-lactam antibiotics were prescribed as per the guideline-recommended treatment duration - 42% of patients with an uncomplicated or complicated cystitis and treated with guideline-congruent empiric antibiotic therapy had negative urine cultures
Poole et al., (2019)	Cross-sectional retrospective study, NHAMCS, non-federally-employed, office-based physicians primarily engaged in patient care, emergency departments and outpatient departments of non-federal general and short-stay hospitals, condition specific	Not stated	5 years	- Acute respiratory tract infections - UTI - SSTI - Other conditions	- Penicillin: narrow spectrum (40%) - Penicillin: broad spectrum (10%) - Cephalosporin: first generation (10%) - Cephalosporin: second to fourth generation (14%) - Macrolides (17%) - Sulphonamides (9%) - Clindamycin (3%) - Fluoroquinolones (2%) - Tetracyclines, urinary anti-infectives, aminoglycosides (3%)	- 23% of annual ED visits by children received antibiotics - Percentage of ED visits resulting in an antibiotic prescription was significantly higher in non-paediatric EDs compared with paediatric EDs - Acute respiratory tract infections mostly resulted in antibiotics (55%), followed by SSTIs (9%) and UTIs (7%) - 32% of paediatric ED visits nationally that resulted in antibiotic prescriptions were for conditions where antibiotics are generally not indicated - Non-paediatric EDs had significantly more antibiotic prescriptions for diagnoses for which antibiotics are generally not indicated compared to paediatric EDs - AOM, sinusitis, or pharyngitis diagnoses: 78% of visits received first-line, guideline concordant antibiotic therapy

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study time period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Prusakowski and Kuehl, 2015	Cross-sectional surveys: NHAMCS, non-federally-employed, office-based physicians primarily engaged in patient care, emergency departments and outpatient departments of non-federal general and short-stay hospitals, condition specific	Not stated	3 years	SSTI	- Trimethoprim/ sulfamethoxazole - Clindamycin - Doxycycline - Vancomycin - Cephalexin	- average of 10% of patients over the 4-years were given antibiotics in the ED but not given at discharge, which may be further provision of inappropriate use - range of 71.8% to 75.5% of discharged patients were given antibiotic prescriptions for the care of their abscesses after incision and drainage was significant and consistent throughout the study period - Many patients received multiple antibiotics
Timbrook et al., 2017	A retrospective chart review, ED of single teaching hospital	159	1 year	- Bronchitis or URTI - CAP - COPD - Flu - Intra-abdominal infections - Prophylaxis - SSTI - UTI	- Antiviral (5.0%) - Clindamycin (2.5%) - Cephalosporin (17.6%) - Fluoroquinolone (17.0%) - Macrolide (20.8%) - Metronidazole (5.0% - Penicillins (22.6%) - Sulphonamide (2.5%)	- 39% of antimicrobial prescriptions were inappropriate - Inappropriate prescribing varied by indication: CAP (33.3%), bronchitis/URTI (28.9%), SSTI (25.6%), intra-abdominal infections (15.0%), UTI (25.0%) and other conditions (28.6%) - 49.7.8% of prescriptions with an appropriate indication, but 13.8% had inappropriate prescribing of dose, duration or expense - Inappropriate dosage: CAP (11.1%), UTI (12.5%) - Inappropriate duration: bronchitis/URTI (6.0%), SSTI (7.7%), of intra-abdominal infections (5.0%) - Excessive expense: 11.1% of CAP, 2% of bronchitis/URTI

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study time period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Walsh et al., 2019	Retrospective analysis of electronic health records, condition specific, two primary care practices within Allegheny Health Network	911	1 year	- Rhinosinusitis - Pharyngitis - Acute nasopharyngitis - Acute laryngitis or tracheitis - Acute URTI - Acute bronchitis - Influenza	- Not stated	- 28.4% received antibiotics where they were not indicated - Inappropriate antibiotic prescribing occurred in 21.4% for conditions where antibiotics are always inappropriate - Antibiotics prescribed without an indication: rhinosinusitis (59.4%), pharyngitis (24.4%) - Indicated antibiotic prescriptions for rhinosinusitis: 52.4% appropriate duration, 73.3% appropriate agent, 28.6% optimal prescribing - Indicated antibiotic prescriptions for pharyngitis: 78.3% appropriate duration, 47.8% appropriate agent, 52.2% optimal prescribing
Wattengel et al., 2019	Retrospective chart review, condition specific, outpatient settings (emergency department, primary care clinics, homebased primary care, or community-based outpatient clinics) of VA Western New York Healthcare System	518	10 years	CAP	- Azithromycin (45%) - Fluoroquinolones (38.2%) - Doxycycline (10.0%) - Beta-lactam plus atypical agent (azithromycin or doxycycline) (2.3%)	- 30.8% of CAP diagnoses were prescribed an IDSA guideline consistent antibiotic regimen - Inappropriate antibiotic regimens due choice of antibiotic (76.7%), duration (39.4%) and dose (5.1%) - 53% of appropriate CAP diagnoses received an incorrect antibiotic - Inappropriate antibiotic selection: azithromycin (64%), doxycycline (18%) and fluoroquinolones (11%) - 3.5% of appropriate CAP diagnoses were prescribed incorrect dosing - 27% of appropriate CAP diagnoses were

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study time period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
						prescribed inappropriate duration, mostly prolonged - Inappropriate drug choice was associated with higher rates of late treatment failure - Appropriate regimen did not affect factors of mortality
Wattengel et al., 2020	Retrospective chart review, condition specific, outpatient settings (emergency department, primary care clinics, and community-based outpatient clinics) of VA Western New York Healthcare System	607	13 years 3 months	UTI	- Fluoroquinolones (61.2%) - Trimethoprim/sulfamethoxazole (21.7%) - Beta-lactams (13.2%) - Doxycycline - Ciprofloxacin or levofloxacin - Moxifloxacin - Nitrofurantoin - Linezolid	- Antibiotic therapy was indicated in 68.2% of patients - If a patient received inappropriate empiric antibiotics, were 5.3 times more likely to receive an antibiotic when not indicated - Patients who did not have urinalysis were 3.9 times more likely to receive unnecessary antibiotics - Patients who did not have imaging done were 2.1 times more likely to receive antibiotics when not indicated - Inappropriate regimens consisted of 50.9% of incorrect durations, 35.1% of incorrect antibiotic choices and 12.4% of incorrect doses - 10% of patients had a reinfection within 30 days - 5.1% of patients had a recurrence of UTI with the same pathogen within 30 days - 3.5% of patients readmitted within 30 days for UTI

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
White et al., 2019	Prospective observational cohort study, outpatient settings (ED, or community-based outpatient clinics) of VA Western New York Healthcare System	1063	4 months	- Bronchitis - CAP - COPD exacerbation - Diabetic foot - Epididymitis - Otitis media - Pharyngitis - Prostatitis - Sinusitis - SSTI - STI - URTI - UTI	- Amoxicillin/clavulanic acid (15.7%) - Amoxicillin (6.3%) - Azithromycin (27.1%) - Beta-lactam + trimethoprim/ - sulfamethoxazole (2.4%) - Beta-lactam + atypical (azithromycin/ doxycycline) (0.5%) - Cefdinir/cefpodoxime (4.1%) - Cephalexin (13.2%) - Ciprofloxacin (13.0%) - Clindamycin (0.2%) - Fluoroquinolone + metronidazole (1.4%) - Levofloxacin (3.1%) - Miscellaneous (0.4%) - Moxifloxacin (3.4%) - Trimethoprim/ sulfamethoxazole (9.3%)	- Antibiotics were inappropriately prescribed in 40% of patients - 25% of cases the duration of antibiotic prescribed was inappropriate - 19% of cases the dosing was inappropriate - The most common indications resulting in unnecessary antibiotics: UTIs (21%), bronchitis (20%), SSTI (17%), sinusitis (10%) - UTIs: 54.9 % correct drug choices, 70.5% correct doses, 52.9% correct duration, 54.4% prescribed for indication consistent with guideline diagnostic criteria - SSTI: 58.2 % correct drug choices, 72.1% correct doses, 87.5% correct duration, 73.9% prescribed for indication consistent with guideline diagnostic criteria - Respiratory infections/ear, nose, throat infections: 42.6 % correct drug choices, 88.4% correct doses, 78.6% correct duration, 52.5% prescribed for indication consistent with guideline diagnostic criteria - Most commonly prescribed unnecessary antibiotic: azithromycin (37%), ciprofloxacin (16%), amoxicillin/clavulanate (13%), cephalexin (12%).

Table 13: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within the USA continued.

Authors, year	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Zatorski et al., 2016	Single centre, prospective, observational study, condition specific, in an urban, academic ED in a tertiary care hospital	103	17 months	- Pyelonephritis - Cystitis	- Ciprofloxacin (59.2%) Nitrofurantoin (20.4%) - Trimethoprim/ Sulfamethoxazole (18.4%) - Other (1.9%)	- 63.1 % patients who received antibiotic treatment that did not adhere to the 2010 International Clinical Practice Guidelines (ICPG) guidelines - 62.7 % of patients with cystitis received treatment non-adherent to the guidelines - Reasons for non-adherent treatment in cystitis: inappropriate use of a fluoroquinolone (97.6 %) - 19.4 % of patients with uncomplicated cystitis received the first line agent of nitrofurantoin - 63.9 % of patients with pyelonephritis received treatment non-adherent to the guidelines - Reasons for non-adherent treatment in pyelonephritis: inappropriate antibiotic choice and no initial intravenous antibiotic - Physicians were more likely to be guideline non-adherent for patients with no recent history of UTI, had cystitis with back or abdominal symptoms only or had cystitis with vaginal discharge

Table 15: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Europe.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
García-Moreno et al. 2022	Spain	Observational, descriptive, retrospective study, paediatric ED of a tertiary care hospital	648 care episodes	1 year	- Acute otitis media - Acute pharyngitis/ tonsillitis - Conjunctivitis - Pneumonia - UTI - URTI - Gastroenteritis - Laryngitis - Bronchiolitis	- 165 out of 648 (25,5%) cases received antimicrobial treatment, but 23 cases treated with an antimicrobial could not assessed - 156 cases received antibiotics - 8 cases received antifungals - 1 case received an antiparasitic agent - 73.3% were prescribed penicillins: amoxicillin in 60.6%, amoxicillin/clavulanic acid in 12.1% and penicillin V in 0.6%	- 88% (550/625) of cases, antibiotic therapy was considered appropriate in every aspect according to published guidelines (indication, selection, dose, dose interval, duration of treatment and route of administration) - 0.5% of cases were inappropriate due to failure to prescribe antimicrobial in which it was indicated according to published guidelines - 5% of cases were inappropriate due to unnecessary antibiotic prescription according to published guidelines - 49.3% (70/142) of cases when an antimicrobial was prescribed were appropriate according to published guidelines - 44.4% of UTI cases were appropriate according to published guidelines - 50% of conjunctivitis cases were appropriate according to published guidelines - 52.2% of otitis media cases were appropriate according to published guidelines - Increased probability of unnecessary antimicrobial prescription according to published guidelines in patients under 2 years (16/59 episodes) compared to older children and adolescents (15/106 episodes)
Guzmán Molina et al., 2014	Spain	Single centre, retrospective medical report	15094	26 months	URTI: - Colds - Acute otitis media	- Amoxicillin - Amoxicillin/clavulanic acid	- Antibiotic therapy was prescribed in 30.8% of URTI: 5.7% in rhinopharyngitis, 96.5% in acute otitis media and 36.7% in tonsillopharyngitis

Table 14: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Europe continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
		review, condition specific, paediatric ED of a secondary university general hospital			- Tonsillopharyngitis LRTI: - Acute bronchitis - Bronchiolitis - Laryngitis - Pneumonia	- Cephalosporins - Azithromycin - Clarithromycin	diagnoses - Antibiotic therapy was prescribed in 12.4% of LRTI 9.4% revisit to the emergency department for the same reason within one week - Antibiotic prescriptions for acute otitis media were in line with published international recommendations - Antibiotic prescriptions for pneumonia were in line with general recommendations - Beta-lactam antibiotics prescribed in over 70% of cases
Grenet et al., 2016	France	Retrospective monocentric study, ED of a teaching hospital	760	1 year	- UTI - Cutaneous infections - Respiratory tract infections - ENT infections	Classes: - Penicillins (41.8%) - Fluoroquinolones (40.83%) Individual: - Amoxicillin/clavulanic acid (31.85%)	455 prescriptions (59.86%) were associated with inappropriate antibiotic treatments according to guidelines: - absence of an indication for antibiotic therapy (40.7%) - inadequate spectrum of activity (19.62%) - excessive treatment duration (17.97%) - excessive doses (3.3%) Rates of inadequate prescriptions according to condition: - 82.26% for ENT infections - 71.2% for cutaneous infections - 46.53% for respiratory tract infections - 38.4% for UTIs Inappropriate prescriptions were associated with

Table 14: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Europe continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
							amoxicillin/clavulanic acid (39.39%) and fluoroquinolones (31.38%) Rates of inadequate prescriptions according to antibiotic: - 100% of metronidazole prescriptions - 74.28% of Amoxicillin/clavulanic acid prescriptions - 71% of cephalosporin prescriptions - 63.63% of pristinamycin prescriptions - 59% of amoxicillin prescriptions - 50% of macrolide prescriptions - 46.18% of fluoroquinolone prescriptions
Lalande et al., 2018	France	Single centre, prospective, observational study, paediatric ED if a university hospital	11573	5 months	Not stated	Not stated	- Antibiotics made up 30.4% of all medicine errors - Amoxicillin was frequently involved in errors - Antibiotic treatment errors: overdosing, underdosing, calculation errors, lack of knowledge, antibiotic choice errors, omission errors and pharmaceutical form errors

Table 16: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Asia.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Alanazi et al., 2015	Saudi Arabia	Cross-sectional study, ED of a public district hospital	5752	3 months	- Respiratory tract infections - UTIs - Otitis media - Dermatological infections - Gynaecological-related infections - Gastrointestinal infections	- Penicillin (35.8%) - Cephalosporin (30.1%) - Macrolide (20.1%) - Quinolone (11.1%)	- 46.2% inappropriate antibiotic prescriptions - 2% selection error - 4.2% frequency error - 21.7% dosage error - 28.6% duration error - 97.1% of gastrointestinal, 57.4% of middle ear, 50.5% of skin, 48.6% of urinary, 42.2% of respiratory and 7% of obstetrics and gynaecology infection cases with inappropriately prescribed antibiotics
Ata et al., 2018	Bangladesh	Cross sectional study, outpatient department in a tertiary medical college hospital	300	6 months	- Not stated	- 79% prescriptions had one antibiotic - 19.6% prescriptions had two antibiotics - 0.7% prescriptions had three antibiotics - Cefuroxime (22.5%) - Azithromycin (11.6%) - Cefixime (11.5%) - Ciprofloxacin (10.9%) - Flucloxacillin (10.9%) - Metronidazole (8.7%)	- Only 52.9% of antibiotics were prescribed from EDL by the WHO - 19.71% of injectable antibiotics prescribed higher than WHO recommended 10% or less

Table 15: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Asia continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Fahs et al., 2017	Lebanon	Retrospective observational study, condition specific, ED in three hospitals	258	6 months	- CAP - UTI - Sepsis - SSTI	- Carbapenems (32.6%) - Fluoroquinolones (32.6%) - Cephalosporin (30.2%) - Penicillins (24.4%) - Macrolides (10.5%) - Other antibiotics (12.8%) - Aminoglycosides (8.1%) - One antibiotic prescribed (51.2%) - Two antibiotics prescribed (46.5%) - Over two antibiotics prescribed (2.3%)	- 32.6% adherence to international guidelines - 28.3% CAP antibiotic prescriptions adhered to guidelines - 28.6% sepsis antibiotic prescriptions adhered to guidelines - 40% UTI antibiotic prescriptions adhered to guidelines - 50% SSTI antibiotic prescriptions adhered to guidelines - Beta-lactam prescriptions adhered least to guidelines - 53.5% of cases were incorrect antibiotic choice - 36.2% of cases were incorrect antibiotic choice and dosing - 10.3% of cases were incorrect antibiotic dosing
Tagashira et al., 2019	Japan	Retrospective cohort study, ED at a tertiary care centre	1555	12 months	- Pneumonia - Animal bite - Intra-abdominal infections - UTI - Pharyngitis - SSTI - Gastroenteritis	- Penicillins (42.9%) - Cephalosporins (23.4%) - Fluoroquinolones (13.6%) - Trimethoprim/ sulfamethoxazole (8.2%) - Macrolides (5.3%) - Clindamycin (0.7%) - Tetracyclines (0.4%)	- 52.3% of antimicrobial prescriptions indicated misuse of antimicrobials - Unnecessary discharge antimicrobial prescriptions accounted for 27.5% of cases - Inappropriate discharge antimicrobial prescriptions accounted for 21.7% of cases - Suboptimal discharge antimicrobial prescriptions accounted for 3.1% of cases

Table 15: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Asia continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
					- Composite URTI: acute tonsillitis, acute otitis media, otitis externa, sinusitis, bronchitis, asthma attack - STI - Prophylaxis for traumatic injury - Odontogenic infection - Sialadenitis - Febrile neutropenia - Lymphangitis - Bursitis - Septic arthritis - Tonsillar abscess	- Metronidazole (0.2%) - Fosfomycin (0.2%) - Penicillins + macrolides (3.5%) - Penicillins + fluoroquinolones (0.5%) - Cephalosporins + clindamycin (0.3%) - Fluoroquinolones + metronidazole (0.3%) - Trimethoprim/ sulfamethoxazole + metronidazole (0.1%) - Fluoroquinolones + clindamycin (0.1%) - Double fluoroquinolones (0.06%) - Amoxicillin + minocycline (0.06%) - Amoxicillin + trimethoprim-sulfamethoxazole (0.06%) - Cephalexin + trimethoprim/ sulfamethoxazole (0.06%) - Cephalexin + minocycline (0.06%) - Minocycline + metronidazole (0.06%) - Trimethoprim/ - sulfamethoxazole + levofloxacin (0.06%)	- Misuse occurred most often in UTI, SSTI, prophylaxis for traumatic injury and composite URTI

Table 15: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings within Asia continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescriptions
Wang et al., 2020	China	Prospective, cross-sectional survey, outpatient and emergency departments of 16 public tertiary hospitals	260 001	12 months	- Non-infectious diagnoses - URTIs - Bronchitis/bronchiolitis - Pneumonia - Undifferentiated fever - Diarrheal illness - Cough - Herpangina - Possible group a streptococcus infection	Most common: - Azithromycin (15.4%) - Cefdinir (10.6%) - Cefixime (9.1%) - Ceftizoxime (6.7%) - Cefaclor (6.6%) - Cefprozil (5.2%) - Amoxicillin and b-lactamase inhibitor (4.3%) - Cefpodoxime (3.9%) - Ceftazidime (3.8%) - Cefathiamidine (3.6%)	- 36.3% of paediatric encounters in outpatient and emergency departments, antibiotics were prescribed - Broad spectrum antibiotics listed in the 2019 WHO Watch group were widely used among paediatric outpatients Overuse of antibiotics was prominent in general hospitals - Nearly 90% of the antibiotics prescribed are classified as Watch group or not recommended by the WHO
Zeng et al., 2016	China	Prospective, cross-sectional study, paediatric ED of university hospital	500	10 days	- Wheezy bronchitis, - URTI - Tonsillitis - Pneumonia - Diarrhoea	- Cephalosporins (75.3%) - Penicillins (22%)	- 62% of patients received antibiotics - 87% of patients with tonsillitis and 25% of patients with an URTI received antibiotics - Antibiotic use for children with an upper respiratory tract infections or tonsillitis was greater than the 20% maximum recommended by the European Surveillance of Antimicrobial Consumption

Table 17: Published research articles assessing appropriateness of antimicrobial prescriptions in emergency care settings in Australia.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescription
Birdsey et al. 2016	Australia	Retrospective cohort study, condition specific, ED of tertiary referral centre	160	12 months	- Dog bite - Cat bite - Human bite - Rodent bite - Possum bite - Ferret bite - Monkey bite	- Antibiotics were prescribed in 89 patients (55.6%) - Piperacillin/tazobactam intravenously (31.3%) - Amoxicillin/clavulanic acid orally (13.1%)	- 61.9% of cases adherent to guidelines - 18.7% of cases where antibiotics choice was not according to guidelines - 11.9% of cases required an antibiotic, but did not receive - 7.5% of cases received antibiotics that were not indicated
Clemence et al., 2018	Australia	Case vignette survey, ED of a hospital	58	4 months	Not applicable	Not applicable	- 54% of antibiotic choices were optimal according to the guidelines - 18% of choices were adequate - 16% of choices were suboptimal - 100% appropriate choices for uncomplicated UTIs - 77% appropriate choices for severe pyelonephritis - 69% appropriate choices for severe cellulitis - 42% appropriate choices for moderate CAP - 69% appropriate choices for sepsis of unknown origin
Denny et al., 2019	Australia	Retrospective, observational study, ED of public tertiary hospital	7497	4 weeks	Not stated	Not stated	- 65.8% antibiotics were appropriate and 34.2% were inappropriate as per four experts with evidence-based guidelines, a pre-established antibiotic appropriateness assessment tool and the National Antibiotic Prescribing Survey table - Conditions with over 30% inappropriate antibiotic regimens: dental conditions (61.5%), ENT (55.2%), CNS (33.3%) and respiratory (32.5%)

Table 18: Published research articles assessing appropriateness of antimicrobial prescriptions in outpatient settings within Africa.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescription
Mashalla et al., 2017	Botswana	Retrospective, cross-sectional study, 19 urban primary health facilities	550	1 year	- Acute tonsillitis - Pharyngitis - Acute laryngitis and tracheitis - Asthma - URTI - Aspiration pneumonia - Bronchitis - Wounds - Boils and abscesses - Herpes zoster - Chickenpox - Burns - STI - PID - Menstrual disorder syndrome - Orchitis - Post safe male circumcision - Otitis media - Conjunctivitis - Dental caries - Fractures - Enteritis - Acne - Allergic dermatitis - Fibrobullar - Genital warts - Dacryocystitis	- Amoxicillin (28.4%) - Ampicillin (1.0%) - Benzathine penicillin (4.2%) - Cloxacillin (6.9%) - Amoxicillin/clavulanic acid (0.3%) - Crystalline penicillin (0.3%) - Penicillin V (4.2%) - Cotrimoxazole (9.2%) - Ceftriaxone (9.8%) - Chloramphenicol capsules (1.0%) - Chloramphenicol ointment (4.2%) - Doxycycline (7.5%) - Erythromycin (6.2%) - Gentamicin (0.7%) - Metronidazole (14.4%) - Nitrofurantoin (0.3%) - Tetracycline ointment (1.0%) - Gentamicin ointment (0.3%)	- 42.7% prescriptions had at least one antibiotic prescribed - Antibiotics prescribed for 87.0% of conditions were compliant with the International Classification of Diseases

Table 17: Published research articles assessing appropriateness of antimicrobial prescriptions in outpatient settings within Africa continued.

Authors, year	Country	Study design, study site	Sample size	Study period	Identified conditions	Antimicrobial usage (%)	Appropriateness of antimicrobial prescription
Eric and Serges, 2019	Ivory Coast	Descriptive and analytical retrospective study, single-centre, ED of university hospital centre	187	31 days	- Hepatic abscess - Cutaneous allergy - Anaemia - Haemorrhagic stroke - Ischemic stroke - Acute bronchitis - Keto-acidosis coma - Convulsive coma - Acute diarrhoea - Infectious endocarditis - Furunculosis - Febrile gastroenteritis - Hydropneumothorax - Chronic renal failure - Lumbosciatica - Febrile meningoencephalitis - Miliary tuberculous - Malaria - Acute pneumopathy - Hypertensive crisis - Severe Sepsis - Sepsis with skin entryway - Pulmonary tuberculosis	- Amoxicillin/clavulanic acid (42.64%) - Ceftriaxone (27.92%) - Trimethoprim/ - sulfamethoxazole (10.19%) - Gentamycin (7.55%) - Metronidazole (7.17%) - Rifampicin/Isoniazide/ Pyrazinamide/Ethambutol (2.26%) - Ofloxacin (1.89%) - Fusidic acid (0.38%)	- Antibiotic therapy was considered irrelevant in 66.41% of the prescription lines for indication - Antibiotic prescriptions were compliant by route of administration and dosage in 93.96% and 70.57% of the prescription lines, respectively.

Table 17: Published research articles assessing appropriateness of antimicrobial prescriptions in outpatient settings within Africa continued.

Authors, year	**Country**	**Study design, study site**	**Sample size**	**Study period**	**Identified conditions**	**Antimicrobial usage (%)**	**Appropriateness of antimicrobial prescription**
Kilipamwambu et al., 2021	Tanzania	Retrospective cross-sectional study	604	1 year	- URTI - UTI - Diarrhoea - Skin infection - Peptic ulcers	- Amoxicillin (22.7%) - Ciprofloxacin (13.6%) - Metronidazole (11.6%) - Trimethoprim/sulfamethoxazole (9.9%) - Amoxicillin/clavulanic acid (6.5%) - Benzylpenicillin (4.3%) - Ceftriaxone (3.8%) - Ampicillin (2.8%) - Erythromycin (2.6%) - Cefalexin (2.5%) - Nitrofuran (0.6%) - Chloramphenicol (0.2%) - Aminoglycosides (1%)	- 97.6% of the antibiotics adhered to the national essential medicines list - Patients with peptic ulcers had a 4.4-fold higher chance of receiving antibiotics - Patients with diarrhoea had a 2.6-fold higher chance of receiving at least one antibiotic

Appendix F: Amendments to the original MAI for data collection

Table 19: Amendments made to the MAI tool.

Original MAI line items	Amendments made to MAI	Reasons for amendments
1. Is there an indication for the drug? 2. Is the medication effective for the drug? 3. Is the dosage correct? 4. Are the directions correct? 5. Are the directions practical? 6. Are there clinically significant drug-drug interactions? 7. Are there clinically significant drug-disease/condition interaction? 8. Is there unnecessary duplication with other drugs? 9. Is the duration of antimicrobial therapy acceptable? 10. Is the drug the least expensive alternative compared to others of equal quality?	1. How many antimicrobials were prescribed for stated diagnosis? 2. Is there an indication for the antimicrobial in accordance with STG/SAASP/SAMF? 3. Was [specific antimicrobial name] indicated for the specified diagnosis in accordance with STG/SAASP/SAMF? 4. Is the route of administration correct in accordance with STG/SAASP/SAMF? 5. Is the frequency correct in accordance with STG/SAASP/SAMF? 6. Is the dosage correct in accordance with STG/SAASP/SAMF? 7. Are the directions complete and practical in accordance with STG/SAASP/SAMF? 8. Are there clinically significant drug-drug interactions in accordance with STG/SAASP/SAMF? 9. Are there clinically significant drug-disease/condition interaction? 10. Is there unnecessary duplication with other drugs?	• Questions were specified to the specific guidelines where possible because for some conditions the guidelines provide different treatment options and each guideline is available and accepted by prescribers. • The question regarding effectiveness was omitted because effectiveness is assumed if the antimicrobial was indicated in the guidelines. • The number of antimicrobials was added to assessing prescribing patterns for the different diagnoses and some conditions require more than antimicrobial according to the guidelines (such as vaginal discharge syndrome). • The question regarding if the diagnosis indicated an antimicrobial was used to assess whether the diagnosis warranted an antimicrobial or not. This assisted in deciding if an antimicrobial was incorrectly omitted. • In each case where an antimicrobial was indicated and prescribed, the choice of the antimicrobial was assessed whether it was appropriate or not according to the specific guidelines. The treatment of the study population is divided into patients who received antimicrobials and those who did

Table 18: Amendments made to the MAI tool continued.

Original MAI line items	Amendments made to MAI	Reasons for amendments
	11. Is the duration of antimicrobial therapy acceptable in accordance with STG/SAASP/SAMF? 12. Is the drug the least expensive alternative compared to others of equal quality in accordance with STG/SAASP/SAMF? 13. Were antimicrobials prescribed for the differential diagnosis and in accordance with which guideline: STG, SAASP, SAMF? 14. Did the patient revisit the ED within 14 days for the same compliant? 15. Were specimens sent for microscopy, culture and susceptibility tests and what were the results?	not. In either case, the choice to prescribe an antimicrobial or not was similarly appropriate and inappropriate, therefore, adherence to guidelines was not influenced by the presence or absence of an antimicrobial. • The route of administration and frequency questions were added because AMS programmes will assess these factors as well. • The differential diagnosis was added to assess whether the prescriber added antimicrobial cover for it, and if so, following which guidelines. This assisted in exploring prescribing patterns further within the ED. • The question, whether the patient revisited the ED within 14 days for the same complaint, was added to observe whether there was a negative outcome for inappropriate prescribing of antimicrobials according to guidelines. • The question regarding testing of specimens and following results was added to assess the appropriateness of antimicrobial based on presence and susceptibilities of microorganisms.

Appendix G: Positive culture and antimicrobial susceptibility results of urine specimens of patients diagnosed with urinary tract conditions

Table 20: The culture and antimicrobial susceptibility results of urine specimens taken from patients diagnosed with urinary tract conditions.

Suspected diagnosis	Patient characteristics	Microorganism	Susceptible	Resistant	Prescribed antimicrobial/s
UTI	Female, child-bearing age, immunocompetent	*E. coli*	- Nitrofurantoin - Cefotaxime - Ceftriaxone - Gentamicin	- Trimethoprim/ sulfamethoxazole - Ampicillin - Amoxicillin - Amoxicillin/clavulanic acid	- Amoxicillin/clavulanic acid
UTI	Female, child-bearing age, immunocompetent	*E. coli*	- Nitrofurantoin	- Trimethoprim/ sulfamethoxazole - Ampicillin - Amoxicillin - Amoxicillin/clavulanic acid - Ciprofloxacin - Cephalexin	- Amoxicillin/clavulanic acid - Ceftriaxone - Metronidazole

Table 19: The culture and antimicrobial susceptibility results of urine specimens taken from patients diagnosed with urinary tract conditions continued.

Suspected diagnosis	Patient characteristics	Microorganism	Susceptible	Resistant	Prescribed antimicrobial/s
UTI	Male, immunocompetent	*E. coli*	- Amoxicillin/clavulanic acid - Nitrofurantoin - Cefuroxime - Gentamicin	- Trimethoprim/ sulfamethoxazole - Ampicillin - Amoxicillin	- Ciprofloxacin
Catheter-associated UTI	Male, immunocompromised	*P. mirabilis*	- Trimethoprim/ sulfamethoxazole - Amoxicillin - Ampicillin - Amoxicillin/clavulanic acid Cefuroxime	- Ciprofloxacin	- Ciprofloxacin
UTI	Male, immunocompetent	Mixed growth			- Amoxicillin/clavulanic acid
UTI	Male, immunocompetent	*E. coli*	- Amoxicillin/clavulanic acid - Nitrofurantoin - Cefuroxime - Gentamicin	- Trimethoprim/ sulfamethoxazole - Ampicillin - Amoxicillin	- Ciprofloxacin
Catheter-associated UTI	Male, immunocompetent	Mixed growth			- Ciprofloxacin - Metronidazole

Table 19: The culture and antimicrobial susceptibility results of urine specimens taken from patients diagnosed with urinary tract conditions continued.

Suspected diagnosis	Patient characteristics	Microorganism	Susceptible	Resistant	Prescribed antimicrobial/s
UTI	Female, child-bearing age, immunocompetent	*E. coli*	- Trimethoprim/ sulfamethoxazole - Nitrofurantoin - Cefuroxime	- Ampicillin - Amoxicillin	- Nitrofurantoin
UTI	Male, immunocompromised	Mixed growth			- Amoxicillin/clavulanic acid

Appendix H: Signed supervisor-student agreement

Statement of principles for postgraduate supervision

In a context of academic freedom and within a framework of individual autonomy and the pursuit of knowledge, this statement is written in the belief that there is a reciprocal relationship and mutual accountability between supervisor and student

THE SUPERVISOR AND THE STUDENT:

1. Will establish agreed roles and clear processes to be maintained by both parties. In the case of joint supervision, the roles and responsibilities of each supervisor and the student need to be clarified.
2. Will meet regularly and as frequently as is reasonable to ensure steady progress towards the completion of the proposal, research report, dissertation or thesis. This time varies but the normal minimum requirement for face-to-face contact spread across each year of registration is: 10 contact hours for an Honours project, 15 contact hours for a Masters by coursework and research report and 24 contact hours for a Masters by dissertation and a PhD.
3. Will keep appointments, be punctual and respond timeously to messages.
4. Will keep one another informed of any planned vacations or absences as well as changes in his or her personal circumstances that might impact on the work schedule. Unplanned absences or delays should be discussed as soon as possible and arrangements should be made, to catch up lost time.
5. Will ensure that research on animal or human subjects is conducted with prior approval and according to the procedures and the requirements of the relevant Ethics committee.
6. Will both complete Progress Reports on the research project as required/requested by the relevant Faculty Graduate Studies Committee.

THE SUPERVISOR:

1. Undertakes to provide guidance for the student's research project in relation to the design and scope of the project, the relevant literature and information sources, research methods and techniques and methods of data analysis.
2. Will provide guidance at the commensurate NQF level requirements for autonomy and accountability that the student is expected to demonstrate.
3. Has a responsibility to be reasonably accessible to the students.
4. Will be prepared for meetings with the student. This includes being up-to-date on the latest work in his/her area of expertise.
5. Will expect written work as jointly agreed, and will return that work with constructive criticism within a timeframe (a suggestion of 2-4 weeks) jointly agreed at the outset of the research.
6. Will provide advice that can help the student to improve his/her writing. This may include referrals for language training and academic writing. The supervisor will provide guidance on technical aspects of writing such as referencing as well as on discipline specific requirements. Detailed correction of drafts and instruction in aspects of language and style are **not** the responsibility of the supervisor.
7. Will guide the student in the production of a research report, dissertation or thesis. Provision should be allowed for adequate, mutually respectful, discussion around recommendations made.
8. Will assist with the construction of a written time schedule, which outlines the expected completion dates of successive stages of the work.
9. Will encourage the student to present work at postgraduate/ staff seminars/national/international conferences as appropriate.
10. Will assist with the publication of research articles as appropriate.
11. Will discuss the ownership of research conducted by the student in accordance with the University rules on intellectual property, copyright, **guidelines on authorship/co-authorship**, and **policy on research integrity.**
12. Will ensure that the student is aware of the University's Plagiarism Policy, knows what plagiarism is, and what the consequences are for academic dishonesty and violation of research integrity and intellectual property.
13. Will ensure that the student is made aware in writing of the inadequacy of progress and/or of any work where the standard is below par. Acceptability will be according to criteria previously supplied to the student.
14. Has a duty to refuse to allow the submission of sub-standard work for examination, regardless of the circumstances. If the student chooses to submit without the consent of the supervisor, then this should be clearly recorded and the appropriate procedures followed.

THE STUDENT:

1. Takes full responsibility for the research and its successful completion; including managing the process under the guidance of supervisor (s).
2. Will attend such courses and lectures that are compulsory for the degree, and undertakes to catch up fully on any work, lectures and/or assignments, that are missed.
3. Undertakes to work independently under the guidance of the supervisor(s). This includes reading widely and critically to ensure that the seminal **and** current literature pertinent to his/her chosen topic has been identified, consulted and critiqued.
4. Undertakes to work in accordance with the academic standards expected by the University for the commensurate NQF level of qualification.
5. Is obliged to make appointments to consult the supervisor(s) and arrange meeting times convenient to both parties well in advance.
6. Should submit written work for discussion with the supervisor(s) well in advance of a scheduled meeting. The kind and frequency of written work should be agreed with the supervisor(s) at the outset of the research.
7. Written work that is submitted to the supervisor, including final submissions to examiners, should be relatively free from basic spelling mistakes, incorrect punctuation and grammatical errors. Responsibility for the accuracy of language, the overall structure and coherence of the final research report, dissertation or thesis rests with the student.
8. Cannot expect the supervisor to be proof-reader and editor of his/her work or to approve work with any of the weaknesses spelt out in **7** above.
9. Undertakes to heed the advice given by the supervisor(s) and to engage in discussion around suggestions made. Ultimately the student has to take responsibility for the quality, integrity and presentation of the work.
10. Should strive to maintain a focus on his/her research area and to work diligently within the agreed time schedule.
11. Agrees to honour agreements about ownership of the research and in accordance with the University's guidelines and rules in relation to co-authorship, copyright and intellectual property.
12. Will ensure that the work contains no instances of plagiarism, violation of intellectual property and research integrity standards, that all citations are properly referenced, and that the list of references is accurate, complete and consistent.
13. Agrees to work in accordance with the criteria of acceptability as supplied by the supervisor(s).
14. Undertakes not to place the supervisor(s) under undue pressure to submit work for examination until the supervisor is satisfied that it has reached an acceptable, **examinable*** level of quality.

We confirm that we have read and understood this statement and agree to be guided by its principles for as long as we continue to work together.

Name of student: Bronwen Wodrich

Student Number: 1035531

Student's signature:

Name of Supervisor: Stephanie De Rapper

Supervisor's signature:

Name of Co-Supervisor: Zelna Booth

Co-Supervisor's signature:

The broad area of study is: Clinical pharmacy

Provisional submission date is: 12-2022

Degree: Master of Pharmacy

School: Pharmacy

Faculty: Heath sciences

Date: 26-02-2021

Specific agreements pertaining to: ownership, joint publication, funding, confidentiality and disclosures pertinent to the Certificate of Clearance and ETD Form which the student and/or supervisor are required to sign, must be attached to this agreement as and when appropriate and kept in the Faculty Office. In the event of disagreements between the supervisor(s) and student, the parties should act in accordance with the University Grievance Policy.

*Note: **Consent by supervisor**(s) to submit work for examination does NOT guarantee that the work will pass. The appointed examiners assess and determine whether the work is of a passable standard.

(2019/09/30)

Appendix I: Ethics certificate for Bronwen Wodrich

TRREE

Zertifikat

Certificat

Certificado

Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Bronwen Wodrich

a complété avec succès - has successfully completed

Public Health Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

Release Date: 2021/03/05
CID : S0keOkLFdM

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program (5 Credits)
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[REV : 20170310]

Appendix J: Ethics certificates for supervisors, Stephanie Leigh (de Rapper) and Zelna Booth

academic advance

Certificate of Completion

GOOD CLINICAL PRACTICE (GCP) BASIC COURSE

Name	S de Rapper
Identity/Passport number	8806140006083
Professional membership number	P31922
Date attended	8 & 9 April 2019
Score achieved in assessment	98%
Venue	WHC, 31 Princess of Wales Terrace, Parktown
Facilitator	Sarah Cohen

The Health Professions Council of South Africa approved CPD reference is as follows:

MDB08/025/01/2019	Activity No: 37750	9 CPD Points
MDB08/026/01/2019	Activity No: 37751 (Ethics)	2 CPD Points (Ethics)

This ICH E6(R2) GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors

16 April 2019

Linda Van Rensburg

HEAD: COMMERCIAL OPERATIONS

DATE ISSUED

ICH Guideline for Good Clinical Practice - E6(R2) 9 November 2016/ SA Good Clinical Practice Guidelines – 2nd Edition 2006

TRREE

Zertifikat Certificado Certificat Certificate

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Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Zelna Booth

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

Release Date: 2022/08/29
CID : RKM0S0Pysv

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

APPROVED BY SIWF FMH ISFM
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[REV : 20220217]

Appendix K: Turnitin report

ORIGINALITY REPORT

15%	11%	11%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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