A REVIEW OF ANTIBIOTIC UTILISATION FOLLOWING THE INTRODUCTION OF AN ANTIBIOTIC PRESCRIPTION CHART IN AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG

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DECLARATION

I, Habibat Salau, 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.

Signature Date

_____ 06/10/2021

DEDICATION

I dedicate this research to my amazing parents, husband and sister for their unwavering support, love and prayers.

ABSTRACT

The global rise in antibiotic resistance, alongside the diminishing research and discovery of new antibiotics, requires the conservation of currently available antibiotics for the management of bacterial infections. Antimicrobial stewardship (AMS) programmes to optimise antibiotic use and improve patient outcomes are being advocated. One such intervention is the use of antibiotic prescription charts. Antibiotic prescription charts have improved antibiotic prescribing in several developed countries, however, information regarding the practice and effects of this AMS strategy on antibiotic usage in South Africa is limited. This study aimed to retrospectively review antibiotic use after introducing an antibiotic prescription chart in a tertiary academic hospital.

This study was a retrospective record review of patients who received antibiotics conducted in an adult infectious diseases ward and a paediatric medical ward at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). Information for a duration of three months was retrieved in the two individual wards before (August to October 2016) and after (August to October 2019) the introduction of the antibiotic prescription chart. These included patient demographics (age, weight, gender), diagnosis, source of infection, prescribed antibiotics per patient, the dosage and frequency of dosing, route of administration, microbial culture and sensitivity, and antibiotic hang time. Data were collected using a revised version of the CMJAH antibiotic prescription chart. The rationale for antibiotic prescribing (prophylactic, empiric or definitive) and whether culture samples were taken before or after initiation of antibiotic therapy were also recorded.

A total of 366 records were reviewed in the adult ward; 200 in the pre-introduction period and 166 in the post-introduction period; while 336 patient records were reviewed in the paediatric ward; 154 in the pre-introduction period, and 182 in the post-introduction period. A statistically significant reduction in the proportion of patients receiving antibiotics from 76.62% in the pre-introduction period to 64.83% in the post-introduction period was recorded in the paediatric ward (p=0.013), while antibiotic prescribing was similar in the adult ward (93.50% vs. 93.98%). A decrease in the mean number of antibiotics per patient was observed in both the adult (2.92 ± 2.30 vs. 2.54 ± 1.62) and paediatric wards (1.60 ± 1.52 vs. 1.31 ± 1.41). Antibiotic regimens of one to seven days were frequent in both study periods across both wards. Overall, there was a 5.07% and 6.78% increase in the proportion of cultures

requested in the adult and paediatric wards respectively following the introduction of the antibiotic prescription chart.

The findings of this study show an improvement in the average number of antibiotics prescribed, duration of antibiotic therapy, the frequency of culture and sensitivity testing and documentation of relevant parameters following the introduction of the antibiotic prescription chart. The use of an antibiotic prescription chart can reduce unnecessary antibiotic use and ensure proper detailing of clinical components necessary for antibiotic selection in a hospital setting.

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LIST OF ABBREVIATIONS

ABR	Antibacterial resistance
AFAs	Antimicrobial feed additives
ALCAPA	Anomalous left coronary artery from the pulmonary artery
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
AS	Antibiotic stewardship
ASP	Antibiotic stewardship programme
AWaRe	Access, watch and reserve
CRP	C-reactive protein
CMJAH	Charlotte Maxeke Johannesburg academic hospital
DAFF	Department of agriculture, forestry and fisheries
DILI	Drug-induced liver injury
ESBL	Extended-spectrum beta-lactamase
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species
FIDDSA	Federation of infectious diseases societies of Southern Africa
HAIs	Healthcare-associated infections
HREC	Human research ethics committee
ID	Infectious diseases
ICU	Intensive care unit
IPC	Infection prevention and control
LRTI	Lower respiratory tract infection
LMICs	Low- and middle-income countries
MDR	Multi-drug resistant
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
NDoH	National department of health
NHLS	National health laboratory service
PCT	Procalcitonin
PDA	Patent ductus arteriosus
PISA	Prevalence of infection in South Africa

SAAHA	South African animal health association
SAASP	South African antibiotic stewardship programme
STG	Standard treatment guideline
TB	Tuberculosis
UGIT	Upper gastrointestinal tract
URTI	Upper respiratory tract infection
US	United States
UTI	Urinary tract infection
VISA	Vancomycin intermediate-resistant *S. aureus*
VRE	Vancomycin-resistant *Enterococci*
VRSA	Vancomycin-resistant *S. aureus*
WHO	World Health Organisation

CHAPTER 1

1. INTRODUCTION

This introductory chapter briefly documents basic information regarding antibiotics and the global challenge of antimicrobial resistance. It also describes the antibiotic prescribing practices in the hospital setting and the rationale for this study. The research question, as well as the study aim and objectives, are also highlighted in this chapter.

1.1 Background

Antibiotics are the most commonly used medicines worldwide with usage rates as high as 50% in hospitalised patients (Owens, 2009; Gelband *et al.*, 2015). The discovery of antibiotics in the mid-20th century came as a breakthrough in the healthcare sector for treating bacterial infections (Shallcross *et al.*, 2015). Before the revolutionary discovery of penicillin by Alexander Fleming, infectious diseases, that are currently treatable, were fatal. Antibiotics have also been of great use in surgical procedures, organ transplants and chemotherapy (Laxminarayan *et al.*, 2016). However, with this invention came the development of microbial resistance to future antibiotic therapy (Junaid *et al.*, 2018).

A global 'post-antibiotic' era is approaching where available and beneficial antibiotics will lose their benefits (NDoH, 2015). This will place a significant social and financial burden on the society as well as an increase in morbidity and mortality, increased cost and prolonged hospital stay (WHO, 2014; NDoH, 2016). Both the appropriate and inappropriate use of antibiotics and improper prescribing are significant contributors to the emergence of resistant bacteria and a waste of health resources, posing a considerable risk for their efficacy in the future (Bronzwaer *et al.*, 2002; Ali *et al.*, 2006; Fishman, 2006; CDC, 2013). The steady rise in antibiotic prescribing in hospitals, especially for nosocomial infections, also aids the development of resistance to antibiotics (Mushtaque *et al.*, 2019). Little is known regarding antibacterial resistance (ABR) in many parts of the world, which makes it more challenging to address this growing public health problem without proper surveillance (WHO, 2014). It is therefore necessary to conserve the efficacy of existing antimicrobials to ensure minimal spread, and development of resistance while endeavours to discover new antimicrobial drugs continue (WHO, 2014).

Antibiotic prescribing is a product of complex interactions of various factors such as individual prescribers' knowledge of antimicrobials and antimicrobial resistance (AMR), attitude, professional experience with antibiotics, prescribers' behaviour and diagnostic doubts in the absence of laboratory findings (Cabana *et al*., 1999; Awad and Aboud, 2015; Bai *et al*., 2016). Factors that influence antibiotic prescribing also include medical diagnosis, patient medical history, the use of national guidelines, patient expectations of receiving an antibiotic or a prescriber-patient relationship (Gill and Roalfe, 2001; Clemence *et al.*, 2018). When Om *et al*. (2016) assessed the attitude, knowledge and practice of physicians from 19 public hospitals in Cambodia in a cross-sectional survey, 54% of the respondents believed that antibiotics were prescribed inappropriately in their hospitals while 93% of them had difficulties in selecting the appropriate antibiotic for the treatment of common infections. A global point prevalence survey evaluating antimicrobial prescribing recorded the highest frequency in Africa (74.7%) and the least in eastern Europe (27.8%) with 34.4% of all patients surveyed receiving at least one antimicrobial agent (Versporten *et al.,* 2018). There are reports of high percentages of antibiotic prescribing in developing countries such as Ethiopia (64.7% of patients in a medical ward of a district hospital) (Gube *et al*., 2017), India (44% of paediatric patients in a private teaching hospital intensive care unit (ICU)) (Sharma *et al.,* 2015) and South Africa (55.2% of patients in ICUs of an academic hospital) (Johnston *et al.,* 2018). The careful and appropriate use of antibiotics is particularly important, not only for optimizing efficacy and minimizing adverse effects but also for reducing the risk of resistance and preserving the value of existing agents (Hooper *et al*., 2018).

The rate of antibiotic prescribing in the South African private sector is estimated to be 73.6% and 72.9% in the public sector (Paruk *et al.*, 2012). A prevalence of infection in South Africa (PISA) study, which documented antibiotic prescribing in private and public ICUs, showed that patients received an average of three antibiotics, with an inappropriate antibiotic given in 60.8% and 43.5% of cases in the private and public sectors respectively (Paruk *et al.*, 2012). The increasing awareness of the current AMR situation worldwide has resulted in the establishment and implementation of AMS interventions (NDoH, 2014). AMS interventions have been instituted and implemented by the National Department of Health of South Africa, due to a surge in multi-drug resistant bacterial infections in South African healthcare institutions (NDoH, 2014).

Infection prevention and control (IPC) programs, alongside antibiotic stewardship strategies, are among the approaches in the fight against antibiotic resistance worldwide (Spellberg *et al.*, 2013). Antimicrobial stewardship was endorsed at the sixty-eighth World Health Assembly of the World Health Organisation (WHO) in a global strategy aimed towards reducing AMR (WHO, 2015). One of the strategic objectives of antimicrobial stewardship is the implementation of an antibiotic prescription chart to promote the rational use of antimicrobials. Studies have documented the benefits of the introduction of dedicated antibiotic prescription charts. Boyles *et al*. (2013) and Junaid *et al*. (2018) observed improved completion of the antibiotic prescription chart in a rural, regional hospital in the Western Cape province in South Africa. This finding could be an indication that all parameters related to prescribing antibiotics were considered before they were prescribed. However, it is difficult to conclude if improved completion of the chart had a positive impact on antibiotic prescribing. Surveillance data is necessary to inform the effectiveness of the antibiotic chart.

In August 2017, a dedicated paper-based antibiotic prescription chart was introduced at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) to improve antibiotic stewardship practices for in-patient cases requiring antibiotics. The antibiotic prescription chart was used to document antibiotics alone at the study site, while other antimicrobials and prescribed medicines are documented on a separate medication prescription chart.

1.2 Research Question

Studies regarding AMS practices in the public sector and the impact of introducing an antibiotic prescription chart in South Africa are scarce. Has the introduction of a paper-based antibiotic chart influenced antibiotic prescribing practices and antibiotic utilisation?

1.3 Aim

This study aimed to retrospectively review the utilisation of antibiotics during the introduction of an antibiotic prescription chart in a tertiary academic hospital in Johannesburg.

1.4 Objectives

The following objectives were outlined to achieve the study aim:

- To retrospectively review antibiotic utilisation before the introduction of an antibiotic prescription chart.
- To retrospectively review antibiotic utilisation after the introduction of the paper-based antibiotic prescription chart.
- To compare antibiotic use before and after the introduction of the paper-based antibiotic prescription chart.

CHAPTER 2

2. LITERATURE REVIEW

2.1 Introduction

This chapter describes AMR and the challenges surrounding it. It also highlights antibiotic utilisation globally, bacteria of global concern and antibiotic stewardship practices developed to optimise antibiotic use; with a focus on the paper-based antibiotic prescription chart and the current situation in South Africa.

2.2 Overview of Antimicrobial Resistance

The earliest discovery of compounds with antimicrobial activities dates back to the twentieth century when Paul Ehrlich discovered the "magic bullet" as a remedy for syphilis (Wright, 2012; Zaffiri *et al.*, 2012). Selman Waksman first referred to the word antibiotic as " *a small molecule made by a microbe that antagonises the growth of other microbes*" in 1941 (Clardy *et al.*, 2007). The first known antibiotic was discovered in 1928 by Alexander Fleming when a mould contaminated a culture plate of staphylococci in his laboratory. Following extensive research and purification, the mould exhibited bacteriostatic, bactericidal, and bacteriolytic properties (Fleming, 1945).

Since their discovery, antibiotics have been of great importance in managing bacterial infections by decreasing morbidity, preventing mortality and increasing life expectancy by up to 20 years (Aminov, 2010; NDoH, 2014). However, Abraham and Chain (1940) reported that resistance to penicillin existed before its adoption in clinical use. Over the years, bacteria have, and are, incessantly developing resistance to the antibiotics they were previously susceptible to. This challenge, coupled with a dry antimicrobial drug pipeline, has made antibiotic resistance a global public health problem (WHO, 2014).

Infectious diseases led to mortality in millions of people for many centuries before the introduction of antibiotics (Zaffiri *et al.*, 2012; Mohr, 2016). Presently, 700,000 deaths are being recorded yearly due to resistant infections, and by 2050, the death toll could escalate to one person every three seconds (O'Neill, 2016), with a 10 million worldwide increase in mortality costing up to 100 trillion dollars (Shallcross *et al.*, 2015). In the United States (US) alone, estimates suggest that about 2 million people develop severe bacterial infections that are unresponsive to the antibiotic treatments intended for these infections; with no less than

23,000 deaths caused by antibiotic-resistant infections annually (CDC, 2013). Antibiotics should be regarded as valuable medicines only to be administered when necessary (Gelband *et al.*, 2015).

AMR arises when microorganisms adapt and thrive in the presence of antimicrobials, rendering treatment with an antimicrobial drug ineffective. AMR threatens the treatment of many hospital and community-acquired, common and life-threatening bacterial infections worldwide, making treatment difficult and impossible in several cases (WHO, 2014; Laxminarayan *et al.*, 2016). AMR is a natural occurrence that dates back to over three decades (D'costa *et al.*, 2011). Microbes are continually evolving and developing new ways of resistance, making antibiotic resistance inevitable (Gould, 2009; Infectious Diseases Society of America, 2010; Wright, 2012). AMR is an outcome of the interactions of several factors including inappropriate antibiotic use, substandard quality of antimicrobial agents, poor IPC, unnecessary empiric therapy (based on the anticipated and likely cause) due to scarce laboratory facilities, supply chain challenges, increased migration of people from one region to another, non-compliance of antimicrobial therapy, and the application of antimicrobial agents in agricultural and veterinary medicine (Duse, 2011). The increase in the rate of bacterial resistance has risen sporadically in many parts of the world which is an indication that most of the available options for the treatment of common infections are losing their potency without replacement (WHO, 2014) and drugs previously reserved for use as the last option are gradually becoming less potent (Leeb, 2004).

The collaboration of local and international bodies, exchange of data and reports on surveillance systems from different countries is necessary for the fight against antibiotic resistance (NDoH, 2016). For every important antibiotic discovered, the development of resistance has been reported as earlier (Table 2.1), and in some cases, within a few months. Current data indicates that Africa is not left out in the global trend of increasing AMR despite the limited surveillance practices to monitor ABR (WHO, 2014).

Table 2.1: Timeline of key antibiotic resistance events as adapted from Centre of Disease Control (CDC, 2013)

Antibiotic	**Year of introduction**	**Resistance discovered**	**Pathogen**
Penicillin	1943	1940 1965	Penicillin-R** *Staphylococcus* Penicillin-R** *Pneumococcus*
Tetracycline	1950	1959	Tetracycline-R** *Shigella*
Methicillin	1960	1962	Methicillin-R** *Staphylococcus*
Gentamicin	1967	1979	Gentamicin-R** *Enterococcus*
Vancomycin	1972	1988 2002	Vancomycin-R** *Enterococcus* Vancomycin-R** *Staphylococcus*
Ceftazidime	1985	1987	Ceftazidime-R** *Enterobacteriaceae*
Imipenem	1985	1998	Imipenem-R** *Enterobacteriaceae*
Levofloxacin	1996	1996	Levofloxacin-R** *Pneumococcus*
Linezolid	2000	2001	Linezolid-R** *Staphylococcus*
Ceftaroline	2010	2011	Ceftaroline-R** *Staphylococcus*

*PDR - Pan-drug-resistant **R – Resistant ***XDR - Extensively drug-resistant

2.2.1 Antimicrobial resistance in South Africa

South Africa has a high incidence of bacterial infections (Crowther-Gibson *et al.*, 2011). However, information regarding the burden of infectious diseases and treatment options in the country is inadequate (Crowther-Gibson *et al.*, 2011). The severity of the AMR crisis in developing countries, including South Africa, is weighty and worsened by the limited availability and affordability of antimicrobials essential in the treatment of resistant organisms (Duse, 2011). Furthermore, surveillance data suggest that resistance continues to rise in prevalent infectious pathogens (NDoH, 2016). The first African reported occurrence of carbapenemase-producing bacteria which is a leading cause of extreme drug resistance worldwide was in 2011 from South Africa (Brink *et al.*, 2012). The increasing frequency of resistance mechanisms exhibited by Extended-spectrum beta-lactamase (ESBL) producing pathogens to multiple antibiotics has also become a challenge in South Africa (Bamford *et al.*, 2011; Fourie *et al.*, 2018). A cross-sectional survey of primary care prescribers in the South African private sector revealed that 97.1% of prescribers thought that antibiotics are misused, and 95.8% believed that the burden of antibiotic resistance is a significant crisis in the country (Farley *et al.*, 2018).

2.2.2 Mechanisms of resistance

Mechanisms by which microbes develop resistance include antibiotic inactivation, efflux of the antibiotic, target site alteration, circumvention of the target pathway (Schmieder and Edwards, 2012), gene mutation (Martinez and Baquero, 2000), or by gene acquisition from other strains or species (Hegstad *et al.*, 2010), with a possibility of a mutant strain exhibiting more than one of these mechanisms simultaneously (Bax and Griffin, 2012). This eventually leads to the replication of the selected resistant bacteria by either colonisation or causing infection (NDoH, 2016). Table 2.2 summarises bacterial mechanisms of resistance, the antibiotics affected, and their levels of resistance.

Table 2.2: Resistance mechanisms, the affected antibiotics and the extent of resistance (Acar and Röstel, 2016)

Mechanism	**Affected antibiotics**	**Level of resistance**
Efflux	Tetracyclines Macrolides Quinolones	Low
Penetration	β-lactams Chloramphenicol Trimethoprim Tetracyclines	Low
Target alteration	β-lactams Aminoglycosides Macrolides Quinolones Rifampicin Glycopeptides	Variable
By-pass	Sulphonamides Trimethoprim	High
Enzyme detoxification	Aminoglycosides Macrolides β-lactams Chloramphenicol Lincosamide	High

2.2.3 Drivers and factors that contribute to antibiotic resistance

Drug-resistant bacterial strains emerge due to selective pressure by bacteria from improper use of antibiotics in agriculture, human and veterinary medicine (Essack, 2017; Van Boeckel *et al.*, 2014). Factors that influence ABR include:

2.2.3.1 Inappropriate antibiotic use

Approximately half of the antibiotics prescribed are estimated to be unnecessary (CDC, 2013; Wasserman *et al.*, 2015) either due to the absence of an infection, the infection not being caused by bacteria or antibiotics being prescribed for a more extended period than required (Departments of Health and Agriculture Forestry and Fisheries, 2019). Goossens *et al.* (2005) established a significant association between antibiotic use and AMR. Inappropriate antibiotic use allows selection by resistant bacteria, enabling them to overcome the action of the antibiotic and killing sensitive bacteria (Laxminarayan and Chaudhury, 2016; NDoH, 2016). Several studies have reported inappropriate antibiotic prescribing in the hospital setting (Thuong, 2000; Tünger *et al.*, 2000; Erbay *et al.*, 2005; Ohl and Luther, 2011). This inappropriateness is mostly accounted for by the absence of an infection, exceeding the therapeutic duration of treatment, and attempting to eradicate infections in patients with no indication of infection or need for prophylaxis (preventive therapy) (Kunin, 1985; Erbay *et al.*, 2005). Several factors associated with improper antibiotic use include disregarding local antibiograms, the unnecessary use of broad-spectrum antibiotics, therapy directed at contamination or colonisation instead of an aggressive infection, inappropriate surgical prophylaxis and continuing antibiotics when an infection has been treated (Brink *et al.*, 2006). A PISA study in public and private ICUs documented a 72% prevalence of inappropriate antibiotic duration and an inappropriate initial antibiotic prescribed in more than half of patients (Paruk *et al.*, 2012).

Most cases of antibiotic misuse by prescribers do not occur out of ignorance but rather as a result of lack of critical consideration of antibiotic therapy or neglect to discontinue antibiotic/s after the required duration of treatment by physicians, probably due to the volume of patients physicians need to attend to and their busy schedule (Durbin *et al.*, 1981; Drew, 2009).

2.2.3.2 Counterfeit drugs

The quality of an antimicrobial is essential in delivering an adequate dosage that is safe and effective in producing desired therapeutic results. Giving subtherapeutic amounts of the drug could lead to treatment failure and selection by drug-resistant species (Okeke *et al.*, 2005). In several developing countries, cheap medicines with compromised quality are readily available to the public in large quantities and at a lower cost (Horton, 2002; Michael, Dominey-Howes and Labbate, 2014). The use of substandard antimicrobial agents has been associated with adverse drug reactions, therapeutic failure, higher morbidity and mortality, increased costs and the development of antibiotic-resistant bacteria (Kelesidis and Falagas, 2015).

2.2.3.3 Use of broad-spectrum antibiotics

The use of broad-spectrum antibiotics promotes the emergence of resistant pathogens as a result of their activity against an extensive range of bacteria when compared to narrow-spectrum antibiotics that focus on specific infection-causing pathogens (NDoH, 2014). The presumed need to prescribe broad-spectrum antibiotics for suspected pathogens encourages inappropriate antibiotic use, and eventually adds to the burden of resistance (Ohl and Luther, 2011). Local surveillance of pathogens is essential in initiating therapy with broad-spectrum antibiotics because antibiotic susceptibility patterns differ between communities and even units within the same hospital (Brink, 2005). Susceptibility patterns should be employed in initiating prompt, empirical therapy with broad-spectrum antibiotics in patients with nosocomial infections until the causative pathogen is identified (Brink *et al.*, 2006). Restrictions on the excessive use of broad-spectrum antibiotics must be instituted to enable appropriate treatment of infections (Paruk *et al.*, 2012).

2.2.3.4 Self-medication over the counter

Self-medication of antibiotics without a prescription in retail pharmacies is common in several countries worldwide (Napolitano *et al.*, 2013; Awad and Aboud, 2015). In 1997, Van Duong *et al.*, (1997) reported that it was a common practice for individuals with minor illnesses for which antibiotics are unnecessary (mostly cough, sore throat, stomach upsets and diarrhoea) to buy antibiotics freely from pharmacies. Over the counter purchase of antibiotics are not controlled in many parts of the developing world as there are no adequate surveillance measures in place due to inadequate resources (Kotwani and Holloway, 2011). About half the quantity of antibiotics used in households of developing countries, such as Cameroon, Sudan,

Nepal, Bangladesh, Nigeria, Iran and Syria are bought without a prescription (Ocan *et al.*, 2015). A study that evaluated the antibiotic self-medication practice of students in a Nigerian public university reported that 55.83% of them purchased antibiotics over the counter from pharmacies, 32.16% from patent medicine stores, and 14.84% consumed left-overs from previous prescriptions (Olayemi *et al.,* 2010). In China, parents self-medicating their children was observed in 59.4% of respondents and this increased with children's age (Bi *et al.,* 2000). Non-prescription purchase may also be aided by the inaccessibility of adequate healthcare facilities by a significant proportion of the population (Laxminarayan and Chaudhury, 2016).

2.2.3.5 Human population

By nature, organisms in a thriving habitat with necessities for survival will continue to exponentially grow until they either run out of resources followed by starvation or are affected by other factors (Michael *et al.,* 2014). The rapidly increasing human population living in close proximity, and migrating from one part of the world to the other allows for transportation of microbes and pathogens in their human host and serves as avenues for the spread of infectious pathogens to be distributed globally (Michael *et al.,* 2014). The result is an unending cycle of unintentional transmission of resistant organisms to healthy individuals in the community (Lipsitch and Samore, 2002).

2.2.3.6 Agricultural applications

The increase in the human population has led to a higher demand for animal protein (Gelband *et al.,* 2015). An estimated 80% of global antibiotic consumption are employed in animal husbandry, aquaculture and agriculture to prevent (prophylaxis or metaphylaxis) or treat infections, or as growth promoters in animal feed (NDoH, 2014, 2016). The practise of adding antibiotics to animal feed has aided the spread and development of drug-resistant microbes in humans and animals (Van Boeckel *et al.,* 2015). In 2010, antimicrobial utilisation in food and livestock production globally was projected at 63,151 tons and is expected to increase by 67% globally, and up to 99% in BRICS (Brazil, Russia, India, China, and South Africa) countries by 2030 (Van Boeckel *et al.,* 2015). In 2011, the Food and Drug Administration in the United States (US) indicated that food-producing animals accounted for 61% of antimicrobial agents purchased (FDA, 2011).

The city of Johannesburg and its surrounding townships are a prominent hotspot where antimicrobial consumption in animals is common (Van Boeckel *et al.*, 2015). In 2014, 23% of antimicrobials imported in South Africa was for animal use and 26% in 2015 (NDoH, 2018c). The Department of Agriculture, Forestry and Fisheries (DAFF) in collaboration with the South African Animal Health Association (SAAHA) reported that between 2014 and 2015, the most used groups of antibiotics in animals include growth promoters (62%), tetracyclines (17%) and macrolides (11%). The growth promoters include antibiotics not used in humans such as ionophores, flavophospholipol (flavomycin), olaquindox, zinc bacitracin and tylosin (NDoH, 2018c). The influence of antimicrobial feed additives (AFAs) in the development of AMR has been reported (NDoH, 2014) and it is essential to phase out the use of antimicrobials in livestock (Laxminarayan and Chaudhury, 2016).

2.2.4 Economic Burden of Antibiotic Resistance

The exact effect of antibiotic resistance on the global economy is unclear and has not been adequately measured (WHO, 2014). It is, however, estimated that if nothing is done, by 2050, the global economic output as a result of AMR will cost $100 trillion (O'Neill, 2016). The increased cost of diagnostics, treatment, extended hospital stays and means of livelihood will also be affected by AMR (WHO, 2012). In the US, medical expenses of up to $29,000 per patient are accounted for by antimicrobial-resistant infections (Roberts *et al.*, 2009) with total economic costs of up to $35 billion a year (CDC, 2013). Data from Europe showed approximately 25,000 deaths resulting from antibiotic-resistant infections, and costs of up to €1.5 billion annually (EMA and ECDC, 2009). The impact of the burden of resistant infections on the populations in developing countries is greater than in high-income developed countries due to the overstretched healthcare systems (Mendelson, 2015).

2.2.5 Bacteria of concern in ABR

Multidrug-resistant (MDR) Gram-negative pathogens have been encountered in the US and different parts of the world and do not respond to many, and in some cases, all available antibiotics (Ohl and Luther, 2011). 'ESKAPE' is an acronym for AMR pathogens of global importance (listed below) that result in a wide range of hospital-acquired infections in the US (IDSA, 2010) and form part of the surveillance system in South Africa (NDoH, 2018c).

- *Enterococcus faecium*,
- *Staphylococcus aureus*,

- *Klebsiella pneumoniae,*
- *Acinetobacter baumannii,*
- *Pseudomonas aeruginosa,* and
- *Enterobacter* species (IDSA, 2010)

In 2017, ESKAPE pathogens comprised 33% of all positive cultures in hospitals in the South African public sector, the most prevalent being *K. pneumoniae* and *S. aureus*, and subsequently *E. coli and A. baumannii* (NDoH, 2018c).

2.2.5.1 Enterococcus faecium

Enterococci are predominantly non-pathogenic commensal organisms that form part of the gut flora in humans and some animals, food, soil and water (Top *et al.,* 2008) and constitute about 1% of the human intestinal microflora (Sghir *et al.,* 2000). They were once considered harmless, however, are now worrisome pathogens responsible for hospital-acquired infections in humans (Top *et al.,* 2008). *Enterococcus faecium* accounts for 10% of hospital-acquired bacteraemia with an increased mortality risk to infected patients (Pinholt *et al.,* 2014). Their intrinsic resistance and the ability to acquire additional resistant genes makes them challenging to treat (Courvalin, 2006).

Enterococcus faecium is naturally resistant to penicillin compounds (Perovic and Chetty, 2013). Recent South African surveillance data show that 48% of *E. faecium* isolates from a public hospital demonstrated resistance to vancomycin; however, further testing is necessary to confirm this discovery (Perovic *et al.*, 2018; Singh-Moodley *et al.*,2018).

2.2.5.2 Staphylococcus aureus

Staphylococcus aureus is a Gram-positive bacteria naturally occurring in the human microflora of the skin and nose and is mostly responsible for infections of the bone, skin, soft tissue, bloodstream and postoperative wound infections (WHO, 2014). In the 1960s, some strains of *S. aureus* termed methicillin-resistant *Staphylococcus aureus* (MRSA) had acquired resistance to penicillin by obtaining a new gene (mecA) that codes for a penicillin-binding protein (WHO, 2014). Clinical isolates of MRSA have been reported to exhibit resistance to vancomycin, which has been used as a drug of last resort in intermediate (vancomycin intermediate-resistant *S. aureus* [VISA]) and high-levels (vancomycin-resistant *S. aureus*

[VRSA]) (Gardete and Tomasz, 2014; Lee *et al.*, 2018). An estimated 30-60% of *S. aureus* isolates are resistant to cloxacillin (Bamford *et al.*, 2011).

2.2.5.3 Klebsiella pneumoniae

Klebsiella pneumoniae is a Gram-negative bacteria present in the gastrointestinal tract, and may be also found in the urinary tract in humans (Saha, 2019). It has, however, become virulent and has been associated with pneumonia, liver abscesses, urinary tract infections and bacteraemia (Paczosa and Mecsas, 2016). Infections caused by *K. pneumoniae* are predominant in immunocompromised hospitalised patients in ICUs and neonatal care facilities with mortality rates exceeding 50% in the vulnerable population (WHO, 2014). Resistance of *K. pneumoniae* to broad-spectrum penicillins, cotrimoxazole and fluoroquinolones has been reported globally (WHO, 2014).

Klebsiella pneumoniae is the most common pathogen isolated in positive blood specimens in both public and private sectors in South Africa (NDoH, 2018). Between 2012 and 2017, the prevalence of ESBL producing *K. pneumoniae* to 3rd generation cephalosporins was between 63% and 70% (NDoH, 2018). Similar resistance to quinolones has been identified, making carbapenems the only available treatment option to this pathogen (NDoH, 2018). A study in the South African public sector reported 36%, 44% and 59% of *Klebsiella pneumoniae* isolates resistant to ciprofloxacin, piperacillin/tazobactam and gentamicin, respectively (Perovic *et al.*, 2018).

2.2.5.4 Acinetobacter baumannii

Acinetobacter baumannii and *P. aeruginosa* are often regarded as healthcare-associated pathogens (NDoH, 2018c). In 2016 more than 80% of *A. baumannii* isolates from various public hospitals in South Africa were discovered to have developed resistance to carbapenems in an AMR surveillance study (Singh-Moodley *et al.*, 2018). In the same year, over 80% of *A. baumannii* isolates demonstrated resistance to imipenem and meropenem, with increasing resistance levels of 72% and 60% to gentamicin and amikacin respectively as reported from 16 South African public hospitals (Perovic *et al.*, 2018).

2.2.5.5 Pseudomonas aeruginosa

Pseudomonas aeruginosa is a significant pathogen implicated in severe nosocomial infections in ICUs, where there are majorly immunocompromised patients (Sonmezer *et al.*, 2016). The microbe can acquire mobile genetic elements that encode resistance factors, including carbapenemases (Ruppé *et al.*, 2015) with a high morbidity and mortality risk as a result of its resistance to several antibiotics (Sonmezer *et al.*, 2016). South African data from 2017 revealed that 25% and 20% of *Pseudomonas* isolates are resistant to carbapenems and piperacillin/tazobactam respectively (NDoH, 2018c).

2.2.5.6 Escherichia coli

Escherichia coli makes up part of the human and animal intestinal flora (WHO, 2014). It has over time become the leading cause of hospital and community-acquired urinary tract infections, bloodstream infection, intra-abdominal infections, meningitis in neonates, and has been associated with foodborne illnesses worldwide (WHO, 2014). *Escherichia coli* is the second most frequently isolated Gram-negative pathogen found in blood isolates in the public and private health sectors of South Africa (NDoH, 2018c). Antimicrobial surveillance data from the South African public sector indicates that about 30% of *E. coli* isolates are resistant to third and fourth generation cephalosporins (Perovic *et al.*, 2018).

2.3 Hospital-acquired Infections

AMR poses the most significant concern in hospitals (Doron and Davidson, 2011) with approximately one in every seven patients admitted into a South African hospital being vulnerable to a healthcare-associated infection (HAI) (Brink *et al.*, 2006). An average of 7% of patients in developed countries and 15.5% in low- and middle-income countries (LMICs) frequently contract an HAI (WHO, 2011). HAIs have become a global public health problem resulting in patient morbidity and mortality of all age groups, especially in the developing world (Gupta *et al.*, 2011; Sonmezer *et al.*, 2016). These infections are spread through droplets or contact and can be airborne (Brink *et al.*, 2006). Hospitals are an intersection point for factors such as prolonged antibiotic use, susceptible patients, and antibiotic-resistant bacteria, thereby making hospitals both a source and reservoir for multidrug-resistant pathogens (Istúriz and Carbon, 2006). Increasing rates of HAIs caused by pathogens resistant to multiple antimicrobials pose a risk for mortality (Grolman and Richards, 2005; Ohl and Luther, 2011). In the US, 1.7 million infections and 99,000 deaths are as a result of HAIs

annually (Curtis, 2008). In developing countries, the frequency of HAIs was found to be 15.5 per 100 patients (Rosenthal, 2011).

Patient management has been complicated by the emergence of MDR bacteria with increased patient morbidity and mortality (Guerin *et al.*, 2000). Hospitalised patients may often be immunocompromised and pose a high risk of developing MDR-bacterial infection (NDoH, 2014) which mostly include healthcare-associated urinary tract infections, pneumonia and bloodstream infections (Gupta *et al.*, 2011). MRSA, vancomycin-resistant enterococci (VRE) and fermentative Gram-negative *Enterobacteriaceae* are the most frequently isolated hospital MDR bacteria in the developed and developing world and are responsible for the most difficult-to-treat hospital infections (Acar and Röstel, 2016). The problem of AMR is multidimensional and thus requires multiple interventions (Figure 2.1) to reduce the incidence and avoid further spread (Fishman, 2006; Godman *et al.*, 2017).

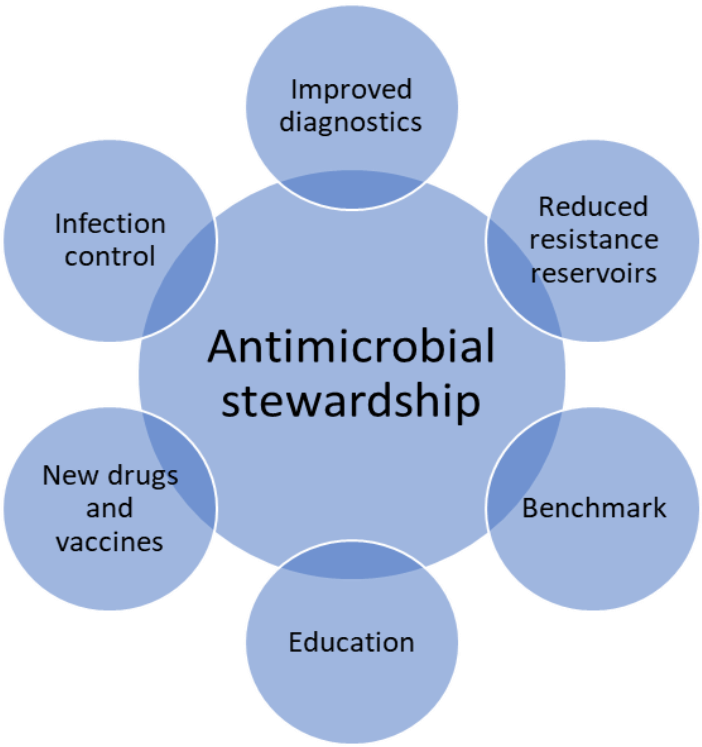

Figure 2.1: Strategies to reduce resistant bacteria. Adapted from (Fishman, 2006)

2.4 Antimicrobial Stewardship

The collective challenges of antimicrobial resistance, the lack of new antibiotics and inappropriate antimicrobial use, as well as the call for the urgent initiation of strategies to

resolve these problems, led to the introduction of antimicrobial stewardship (Van Schooneveld, 2011). Brown and Mitchell (1998) define stewardship as the act of taking responsibility or care or nurturing something. From this, antimicrobial stewardship simply portrays an act of managing and conserving antimicrobials. McGowan and Gerding (1996) first described antimicrobial stewardship (AMS) in an article where the authors called for optimal antibiotic use in response to the rising problem of AMR. The Society for Healthcare Epidemiology of America (SHEA) and Infectious Diseases Society of America (IDSA) jointly published guidelines for developing strategies in institutions to improve AMS in 2007 (Dellit *et al.*, 2007). The US White House in a National Strategy subsequently adopted antimicrobial stewardship programs in 2014 targeted to combat antibiotic-resistant pathogens (The White House Washington, 2015).

The objective of AMS is to encourage responsible antibiotic use with the appropriate dosage and duration of treatment to improve patient outcomes (Drew, 2009). AMS is crucial in the fight against antibiotic resistance (Lowman, 2018) to reduce the advent of resistant microbes, reduce unnecessary drug use, adverse effects and costs (Figure 2.2) (Shlaes *et al.*, 1997; Barlam *et al.*, 2016; Morris *et al.*, 2019). Antibiotic stewardship is a vital responsibility for all antibiotic prescribers and healthcare institutions (Healthcare Infection Control Practices Advisory Committee, 2016).

The introduction of an Antibiotic Stewardship Programme (ASP) could achieve a significant reduction in antibiotic consumption without any negative impact on the patient (Boyles *et al.*, 2017). A combination of an effective AMS programme alongside proper IPC measures has positively impacted the emergence and spread of resistant pathogens by limiting improper antimicrobial use and optimising therapy for patients with infectious diseases (ID) (Dellit *et al.*, 2007; Ohl and Luther, 2011). Three primary targets of antimicrobial stewardship as described by Doron and Davidson (2011) include;

- The collaboration of health care workers and other essential personnel in optimising antimicrobial therapy in patients who require them,
- To discourage antimicrobial overuse, misuse, and abuse,
- To decrease the incidence and spread of resistance.

Antimicrobial stewardship was endorsed in May 2015 at the sixty-eighth World Health Assembly of the WHO, where it was recommended that all member states adopt individual national action plans to combat AMR (WHO, 2015).

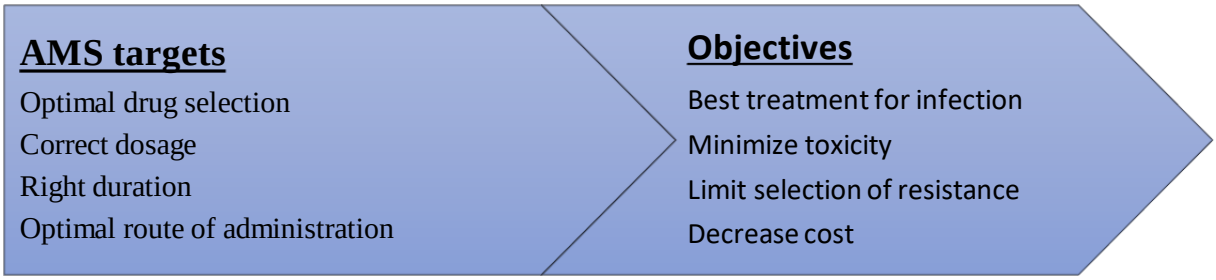

Figure 2.2: Antimicrobial stewardship targets and objectives. Adapted from (Van Schooneveld, 2011)

2.4.1 AMS intervention strategies to combat resistance

AMS strategies are diverse and comprise of interventions such as the restriction of antibiotics, audit and feedback, decision support systems, education and training of the healthcare workforce and are being implemented in many institutions worldwide (Drew, 2009; Charani and Holmes, 2019). The unnecessary extension of the duration of antimicrobial treatment, simultaneous use of antimicrobials with a similar spectrum of activity, neglecting microbial cultures before the commencing empiric therapy and the concurrent administration of over four antibiotics are some antibiotic stewardship initiatives that impact patient outcomes (Messina *et al.*, 2015). However, the direct impact of each specific AMS intervention on bacterial resistance is complicated due to the combination of factors that influence its emergence and spread (Drew, 2009).

2.4.1.1 Prospective audit and feedback (''back-end'' programme)

This involves a post prescription approach where a periodic review of antibiotic therapy is done by an infectious diseases' general practitioner or a clinical pharmacist (with infectious diseases training), with interventions and recommendations to the prescriber if necessary (Doron and Davidson, 2011; Ohl and Luther, 2011). Some benefits of this strategy are that prescribers' autonomy is not restricted and feedback can be a way of enlightening prescribers (Drew, 2009). It also serves as a form of educating prescribers when references and resources that informed the recommendation are provided (Owens, 2009). This strategy had led to an improvement in antibiotic prescribing and use, cost reduction and good clinical outcomes (Fraser *et al.*, 1997; Morris *et al.*, 2019).

2.4.1.2 Formulary restriction and pre-authorisation ("front-end" approach)

Formulary restriction and pre-authorisation involve limiting access to certain recent, high-priced antibiotics in place of older agents of equal efficacy based on guidelines of the AMS committee of individual institutions or prior authorisation of selected antimicrobials by designated personnel to approve such antibiotics when necessary (John and Fishman, 1997; Drew, 2009). This strategy has continually impacted antimicrobial use, resistance and costs (Rapp *et al.*, 2004; Martin *et al.*, 2005). When an antibiotic restriction policy that required prior consultation with an ID specialist for selected antibiotics was introduced in a tertiary hospital in Turkey, improved rational use of restricted antibiotics was observed (Erbay *et al.*, 2005). Formulary restrictions also appeared to be successful in controlling *Clostridium difficile* infections (Muto *et al.*, 2007).

2.4.1.3 Education

The practice of educating and training prescribers on appropriate antibiotic use either through a direct conversation with the prescribers or a formal learning programme is a crucial strategy in AMS (John and Fishman, 1997). Educating prescribers is necessary for passing relevant information to encourage proper antimicrobial usage and should be repeated intermittently as reminders for senior personnel and a guide for new personnel (Drew, 2009). A survey in a large teaching hospital in the US investigated the influence of a one-on-one educational program on broad-spectrum antibiotic prescribing. It concluded that the program was beneficial in reducing inappropriate usage of broad-spectrum antibiotics (Solomon *et al.*, 2001). An educational program should be supplemented with another active AMS strategy to provide a synergistic effect for improved outcomes on antibiotic prescribing practices (Owens, 2009).

2.4.1.4 Guidelines and clinical pathways

This approach involves designing multi-disciplinary, evidence-based guidelines that include local resistance and microbiology patterns (Dellit *et al.*, 2007). Antibiotic treatment guidelines for common infections introduced in a tertiary hospital in Switzerland produced a significant decline in inappropriate antibiotic use after a one year follow up assessment (Deuster *et al.*, 2010). A prospective ICU study by Ibrahim *et al.* (2001) demonstrated that the introduction and implementation of a ventilator-associated pneumonia treatment guideline

reduced the duration of antibiotic therapy and improved antibiotic prescribing in ventilator-associated pneumonia.

2.4.1.5 Antimicrobial cycling

This involves the conscious exclusion and rotation of a specific antimicrobial or class of antimicrobials, to prevent or halt the incidence of resistance to them and may be reintroduced after a specified time (Fridkin, 2003; Dellit *et al.*, 2007). Antibiotic cycling may influence the prevalence of resistant pathogens by reducing the selective pressure of resistant organisms (Brink, 2005). Studies in the ICU setting demonstrated that the initiation of an antibiotic rotation schedule resulted in a gradual increase in well-defined antibiotic prescribing and a decrease in the prevalence of resistant infections (Raymond *et al.*, 2001; Merz *et al.*, 2004). However, results from most studies incorporated another AMS strategy which makes it challenging to establish the actual contribution of antimicrobial cycling only, as well as its influence in limiting the emergence of resistant pathogens (Raymond *et al.*, 2001; Doron and Davidson, 2011).

2.4.1.6 Parenteral to oral conversion

Parenteral to oral conversion involves the switching of antimicrobial therapy of patients from a parenteral route to an oral formulation with equal or enhanced bioavailability once they attain the required criteria, to achieve a decline in the length of hospitalisation, decreased healthcare expenses, and reduced potential complications resulting from intravenous access (Dellit *et al.*, 2007). A pharmacist-led parenteral to oral antibiotic therapy conversion program over a period of 12 months decreased hospital admission significantly by 1.53 days ($p < 0.003$) without compromising patient care, thereby reducing the risk of acquiring an HAI (Przybylski *et al.*, 1997).

2.4.1.7 Streamlining or de-escalation of therapy

Streamlining therapy requires switching an antimicrobial treatment to a directed treatment when culture results become available, or withdrawing empiric therapy if unnecessary (Dellit *et al.*, 2007). Streamlining to monotherapy with penicillin in patients with pneumococcal bacteraemia after a positive blood culture test resulted in a decreased mortality rate (Cremers *et al.*, 2014). In another report by Briceland *et al.* (1988), when antibiotic therapy was reviewed by a clinical pharmacist and infectious disease physician over a period of 7 months,

streamlining of antimicrobial treatment was recommended in 54% of cases resulting in an estimated annual savings of $107,637.

2.4.1.8 Dose optimisation

Dose optimisation involves adjusting antibiotic therapy for individual patients based on features including patient demographics (age, renal function, and weight), site of infection, causative pathogen and pharmacokinetic and pharmacodynamic properties of the medication (Dellit *et al.*, 2007).

2.4.1.9 Antibiotic prescription chart

Durbin *et al*. (1981) first introduced an antibiotic prescription chart, which was also referred to as an antibiotic order form. The antibiotic prescription chart was intended as a method of limiting inappropriate and excessive antibiotic prescribing by encouraging physicians to review necessary clinical and laboratory information before prescribing antibiotics (Durbin *et al.*, 1981; Blok *et al.*, 1996). Physicians were encouraged to indicate their rationale for prescribing antibiotics by categorising them as either prophylactic (preventive), empirical, or definitive (culture-directed) after which the influence of the antibiotic prescription system on the use of antibiotics was reviewed. It was then concluded that the antibiotic prescription system played a significant role in the use of antibiotics as it encouraged physicians to review antibiotic therapy periodically and increased prescribers' consciousness of antibiotic prescribing (Durbin *et al.*, 1981).

In a study involving twenty general hospitals in Pennsylvania, Townsend *et al*. (1979) observed that patients' records mostly did not indicate the reason for antibiotic prescribing and contained conflicting information that varied from patient to patient. The authors subsequently suggested using an order form for easy retrieval and tracing of necessary data. A review of antibiotic usage and nosocomial infections in seven community hospitals observed that only 38% of patients receiving antibiotics had a record of infectious diseases indicated in their files (Scheckler and Bennett, 1970). Echols and Kowalsky (1984) introduced an antibiotic order form for inpatient antibiotic prescriptions in an 800-bed hospital, and this resulted in a significant decrease in the length of antibiotic treatment (p=0.025) and the proportion of patients given antibiotics (p=0.007). A dedicated antibiotic order form is useful

in facilitating surveillance and improving compliance and quality of prescribing (Echols and Kowalsky, 1984; Gyssens *et al.*, 1997).

A weekly AMS ward round in addition to a customised antibiotic prescribing chart introduced in 2 medical wards of a South African academic teaching hospital led to a 19.6% reduction in antibiotic usage, without compromising patient care (Boyles *et al.*, 2013). There was a limitation in the study as the probability that the chart alone resulted in the decreased antibiotic use was not specific with assumptions that the antibiotic stewardship ward rounds were the primary influence. However, it was difficult to isolate the individual impact of the chart or the ward rounds (Boyles *et al.*, 2013).

An antibiotic prescription chart could promote improved prescribing of antibiotics by enabling physicians to familiarise themselves with the appropriate antimicrobial for various infectious diseases, the treatment dosage, duration and the potential to de-escalate antimicrobial therapy when necessary (Blok *et al.*, 1996; Gyssens *et al.*, 1997). An antibiotic prescription chart also helps prescribers to identify the basis for their antibiotic prescribing, to assess the quality of antibiotic prescribing as well as to encourage rational antibiotic prescribing (Moss *et al.*, 1981; Lipsy *et al.*, 1993; Blok *et al.*, 1996). In South Africa, an antibiotic prescription chart (Figure 2.3) was developed by the South African Antibiotic Stewardship Programme (SAASP) (FIDSSA, 2014).

An antibiotic prescription chart is relevant in all stages of the antibiotic prescribing process from patient evaluation to dispensing of antibiotic. It also serves as a converging point for necessary information allowing for the accessibility of essential information to members of the AMS and healthcare team throughout the duration of antibiotic therapy for a patient. The various AMS strategies described come to play in different stages of the antibiotic prescribing process, from patient evaluation to the dispensing of the antibiotic (Figure 2.4).

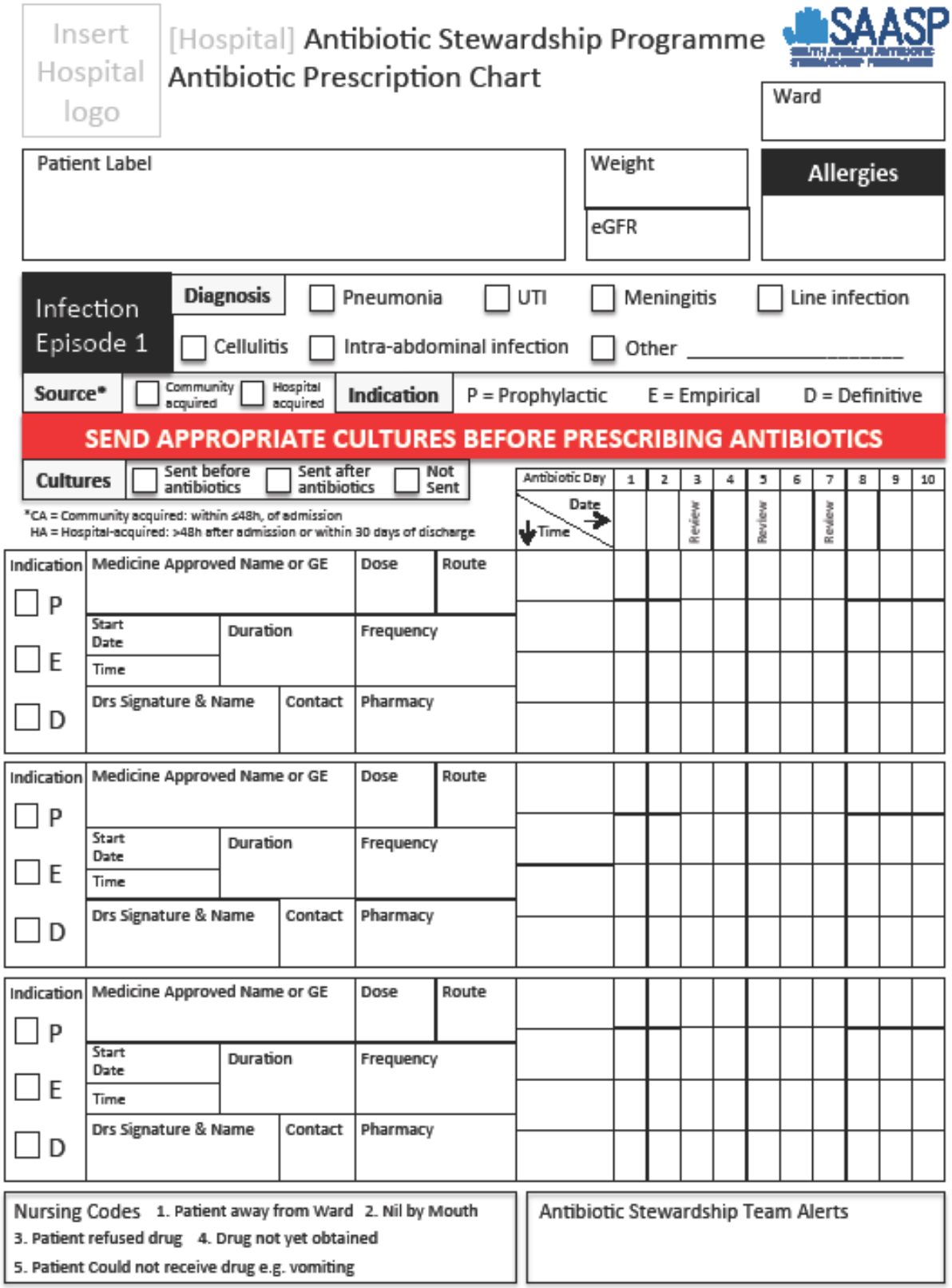

Figure 2.3: SAASP Antibiotic Prescription Chart (FIDSSA, 2014)

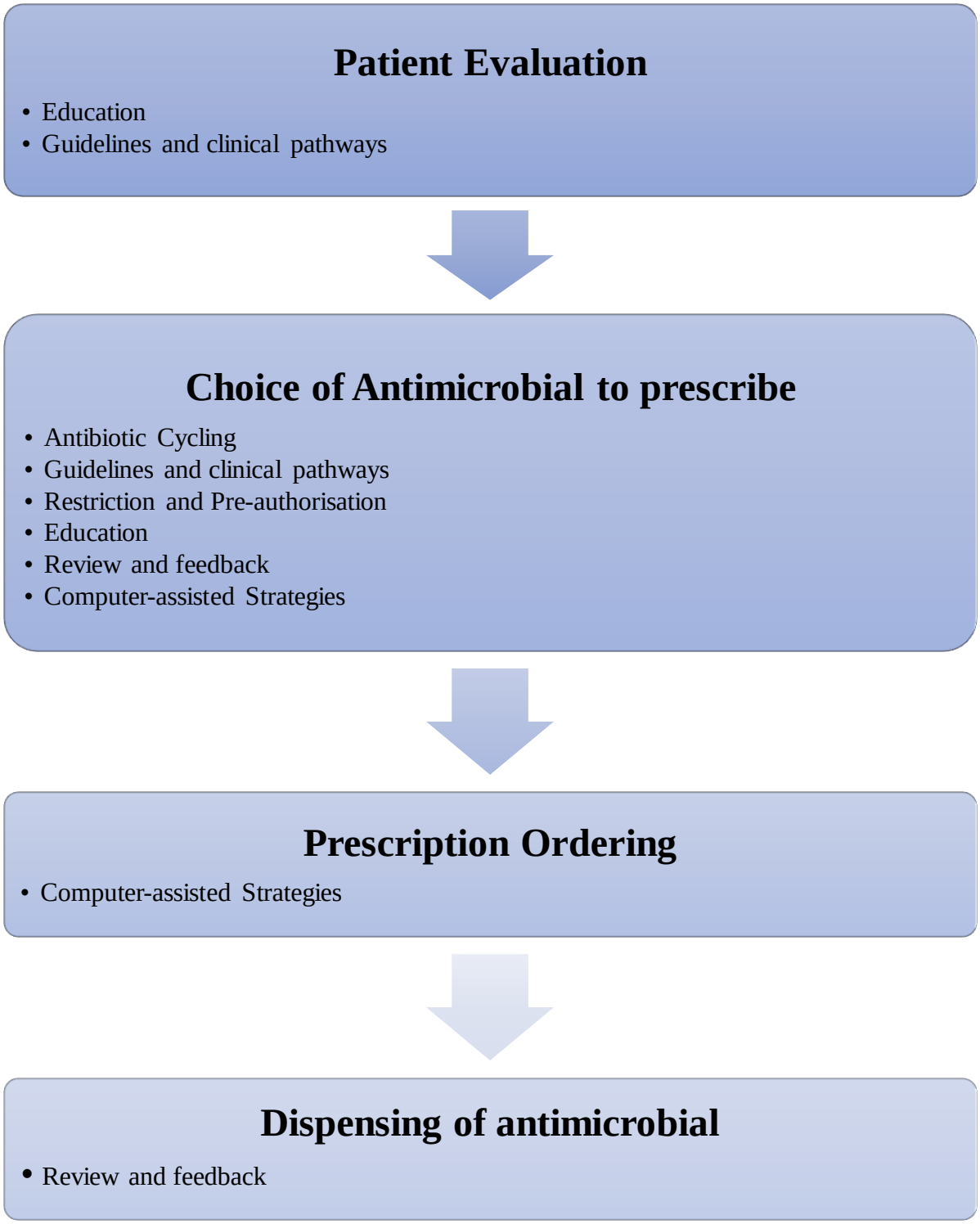

Figure 2.4: Stages of antibiotic prescribing and AMS strategies involved; Adapted from MacDougall and Polk, (2005)

2.5 Antimicrobial Stewardship Team

The goals and strategies of AMS are versatile; hence, the antimicrobial stewardship team is multi-disciplinary (Suleman and Meyer, 2012). Supervision of an AMS programme is overseen by a dedicated infectious diseases physician, who takes responsibility for the design, execution and functioning of the programme and ensures that all AMS practices are evidence-based and will not pose any risk to patients' wellbeing (MacDougall and Polk, 2005). The IDSA/SHEA guideline recommends an infectious diseases physician and a clinical pharmacist with infectious diseases training as the primary team members of an AMS programme (Dellit *et al.*, 2007). Collaboration with personnel from other specialities such as a clinical microbiologist, information technologist, IPC officer, and hospital epidemiologist is essential to achieve an optimal programme (Doron and Davidson, 2011; Suleman and Meyer, 2012). It is also necessary to establish a working relationship with the hospital administration and build an inter-speciality teamwork attitude within the institution for the programme to succeed (Drew, 2009).

2.6 AMS in South Africa

HIV/AIDS poses a risk of acquiring communicable diseases, thus increasing antibiotic use and resistance (Essack, 2017). The South African Department of Health, following the global problem of ABR, adopted an AMR National Strategy Framework as a guideline for the management of AMR in reducing the development of resistant microbial infections, promoting rational use of antibiotics and improving patient outcomes by IPC, surveillance, governance, and antimicrobial stewardship (NDoH, 2014). An implementation plan subsequently followed this framework in 2015, where the adopted strategies were translated to activities with measurable outputs (NDoH, 2015). An implementation study across 47 private South African hospitals suggested that one in every 15 prescriptions required intervention, with a decreased antimicrobial prescribing rate after implementation of an antimicrobial stewardship initiative by non-specialised pharmacists in a resource-limited infectious disease setting (Brink *et al.*, 2016).

SAASP was established in 2012, as part of the Federation of Infectious Diseases Societies of Southern Africa (FIDDSA) following the growing threat of AMR in South Africa; to encourage responsible use of antibiotics, education and engaging with the National Department of Health by uniting necessary skills set experts in the infectious diseases and

veterinary medicine sectors (NDoH, 2016). The current surveillance system on antibiotics is sometimes incomplete and inconsistent as there is no linkage system of clinical and laboratory data in facilities across South Africa (NDoH, 2016).

2.7 Barriers to a Successful AMS Programme

Notwithstanding the numerous benefits of AMS programmes in the improvement of antibiotic use, factors such as lack of funding, shortage of qualified infectious diseases trained pharmacists, the need for continuity of the programme to sustain efforts, and lack of commitment from some staff may hinder the implementation of a well-structured programme (Drew, 2009). A global survey in 2012 from 660 hospitals in 67 countries reported the significant barriers encountered in implementing a successful hospital AMS programme to include lack of personnel and funding, opposition from prescribers as well as lack of information technology support (Howard *et al.*, 2014).

2.8 Antibiotic Utilisation

Annually, an estimated twenty-five million pounds of antibiotics are manufactured for human consumption and administered to 30% to 50% of hospitalised patients (Owens, 2009). Van Boeckel *et al.*, (2014) reported a 35% global increase in antibiotic usage between 2000 and 2010, 76% of which were attributed to BRICS (Brazil, Russia, India, China, and South Africa) countries within that decade. The widespread misuse of antibiotics in humans and livestock has extensively promoted the selection and distribution of resistant bacteria. Subsequently, some antibiotics have lost their potency or even become ineffective, which is a global health crisis that is quickly overwhelming existing treatment options in addition to the numerous current challenges in the effort to contain AMR (WHO, 2014). For existing antimicrobial agents to remain effective in humans, measures to limit the exposure of pathogens to antimicrobials should be taken (Michael *et al.*, 2014). The limited antibiotic treatment options for multidrug-resistant bacterial infections also accounts for the high mortality rates (Aminov, 2010). Therefore, preserving the available treatment options for Gram-negative bacterial infections is crucial (NDoH, 2016).

If infections are prevented by simple measures such as proper hygiene, the immediate need for antibiotics will be eliminated (O'Neill, 2016). Inappropriate antibiotic use is not the only driving force that can lead to resistance, because the spread of resistance is steered by the

exposure of bacteria to antibiotics, whether appropriate or not (Spellberg *et al.*, 2013). Thus, even if antibiotics are used appropriately, antibiotic-resistant infections would still occur, probably at a lower rate (Spellberg *et al.*, 2013). Resistance and possibly treatment failure in a treated host may be as a result of subtherapeutic drug concentrations, limited drug choices, or poor compliance to therapy (Lipsitch and Samore, 2002). The absence of a collaborative regional structure for ABR surveillance in Africa impedes tracking and containment of the emergent resistant organisms and makes it difficult to thoroughly estimate the trends and bacterial resistance-containment activities in the region (WHO, 2014).

2.9 Choice of Antibiotics

When required, the right antibiotic must be selected using the correct dosage, dosing frequency and route of administration, for the appropriate duration and de-escalated when necessary (Wasserman *et al.*, 2015), which Joseph and Rodvold (2008) termed as the "4 D's of optimal antimicrobial therapy" (Figure 2.5).

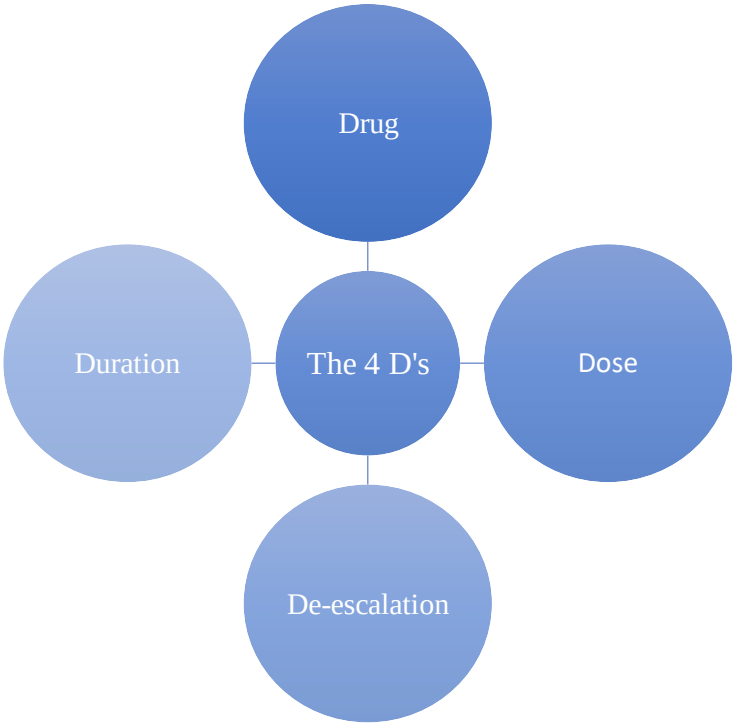

Figure 2.5: The 4 D's of antimicrobial therapy (Joseph and Rodvold, 2008)

Antibiotic selection requires the presence of an infection necessitating antibiotic therapy, features of the patient's symptoms and factors such as age, the severity of symptoms, comorbidities and medical history, to establish that the infection is indeed bacterial in nature

(Slama *et al.*, 2005). Factors such as local susceptibility patterns guided by institutional antibiograms, suspected site of infection and patient-specific factors (infection history, organ function, allergies, antibiotic history) should also be considered before initiating therapy (Allison *et al.*, 2017). Once the need for an antibiotic has been recognised, the right antibiotic with the narrowest spectrum should be selected considering its benefit, safety and cost, and where applicable, monotherapy (Grolman and Richards, 2005; Slama *et al.*, 2005). The duration of treatment with antibiotics should be guided by clinical response (Leekha *et al.*, 2011). General principles for the duration of antibiotic treatment (Figure 2.6) directs that short courses of antibiotics be given, as more extended periods beyond seven days do not show any extra benefit, but rather increase the chances of resistance (Grolman and Richards, 2005; Brink *et al.*, 2006).

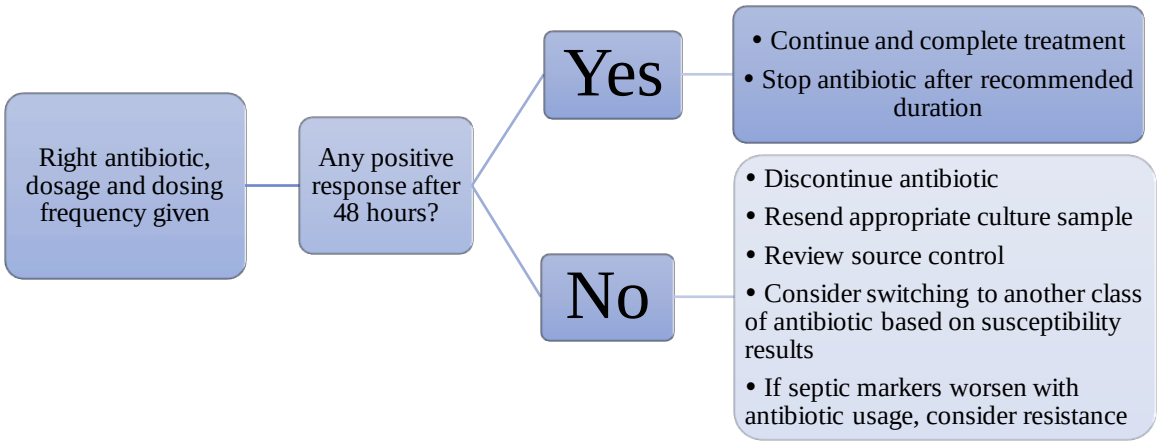

Figure 2.6: General principles for the duration of antibiotic therapy (Brink *et al.*, 2006)

2.10 Culture and Sensitivity Testing

Culture results are essential for antimicrobial stewardship (Pulia *et al.*, 2017). Obtaining appropriate culture samples before the initiation of antibiotics is of great importance in identifying the causative pathogen of an infection for an accurate microbiological diagnosis (Leekha *et al.*, 2011; Allison *et al.*, 2017). Rational prescribing of antimicrobials is only possible if the physician is informed of the potential infective pathogen(s) as many prescribers base their therapeutic choices on the site of infection (Moss *et al.*, 1981). It is critical to define the host (for example., immunocompromised, diabetic, aged), determine the site of infection, and establish, when possible, a microbiological investigation to reach a

diagnosis (Leekha *et al.,* 2011). The outcome of culture results from clinical cultures (blood, urine, cerebrospinal fluid, stool) may be compromised once antimicrobial therapy is initiated before samples are taken (Pulia *et al.,* 2017). The practice of requesting appropriate culture and sensitivity testing should be an avenue to eradicate the problem of ABR and encouraged in all healthcare institutions.

A study conducted by Mabila *et al.* (2016) in the paediatric ward of a public hospital in the Limpopo province of South Africa observed that antibiotics were prescribed based on sensitivity or culture results in only 6.9% of cases and laboratory tests were not requested in 69.7% of cases. Variation in ordering culture tests in ICUs of a tertiary hospital was discovered, with only 56.3% of culture samples taken before or upon the initiation of antibiotic therapy (Johnston *et al.,* 2018). Antimicrobial treatment was guided by microbiology results in only 61.2% of patients in a study of ICUs of a private hospital in KwaZulu-Natal, suggesting misuse (Chunnilall *et al.,* 2015). A drug-bug match is advocated where the prescribed antibiotic is useful for an infection based on antibiotic susceptibility results (Wattengel *et al.,* 2020).

2.11 Antibiotic Hang Time

Antibiotic hang time represents the period between an initial written antibiotic prescription and the time of first administration, which is ideally within one hour (Goff *et al.,* 2017; Schellack *et al.,* 2018). Administering an appropriate antibiotic effective against the causative pathogen within 60 minutes of documented hypotension in patients with septic shock results in a survival rate of 79.9% (Kumar *et al.,* 2006). However, a 7.6% rise in mortality has been associated with each hour delay in administering appropriate antibiotics to patients with sepsis and septic shock (Schellack *et al.,* 2018). Non-infectious disease pharmacists can significantly enhance the timely dispensation of antimicrobials by ensuring the availability of required antimicrobials at the time of administration (Messina *et al.,* 2015).

2.12 The Use of Biomarkers in AMS

Proinflammatory biomarkers have been employed in the identification of infections necessitating the initiation of an antimicrobial agent (Foushee *et al.,* 2012). Clinically, a biomarker is required to provide additional information to supplement established clinical evaluations by accurately differentiating bacterial infection from non-infective and viral

causes, including prompt accessibility and cost-effectiveness (Kibe *et al.,* 2011). Biomarkers such as C-reactive protein (CRP), and procalcitonin (PCT), are commonly used in the detection of infectious and inflammatory diseases (Ahn *et al.*, 2011). Rapid diagnostic biomarker testing at the point of care is essential for prompt initiation of an appropriate narrow-spectrum antibiotic (Laxminarayan *et al.*, 2013).

CRP is an acute-phase plasma protein produced by the liver during systemic inflammation (Sullivan and Von Rueden, 2016). A positive CRP which may indicate the presence of inflammation, however, does not differentiate bacterial from non-bacterial causes (Wasserman *et al.,* 2015). PCT on the other hand has been known to distinguish inflammation of infectious sources from non-infectious ones (Sullivan and Von Rueden, 2016). It has also been reviewed in critical care patients as an aid to effectively shorten the antibiotic duration of therapy in AMS (Kibe *et al.,* 2011). Bacterial infections are better diagnosed with PCT however costs 10 times more than CRP (Wasserman *et al.*, 2015).

2.13 Rationale for Antibiotic Prescribing

An accurate diagnosis for an infectious disease may require multiple laboratory-based tests to identify the causative pathogen which are not often immediately available. A patient who presents with life-threatening symptoms will require immediate action to prevent complications and even death and is mostly prescribed different antimicrobials with different mechanisms of actions with the premise that the pathogen will be susceptible to at least one of them (Michael *et al.,* 2014). After careful examination of a patient and requesting appropriate culture samples for testing, in most cases, results only become available after 24-72 hours which makes initial therapy for infections empiric with broad-spectrum antibiotics, guided by clinical presentation and local antibiograms (Leekha *et al.,* 2011). Appropriate initial antibiotic therapy plays a huge role in reducing mortality in patients with nosocomial infections as a delay of as little as six hours could worsen the clinical outcome for the patient (Brink, 2005). It is essential to initiate empiric broad-spectrum therapy after appropriate cultures have been obtained (Allison *et al.,* 2017). Prescribers should base empiric treatment on the potential pathogens by considering the following factors: site of origin of infection, knowledge of local unit epidemiology patterns, comorbid conditions, allergies, liver and renal functions, and previous antibiotics (Grolman and Richards, 2005). It is also vital that when culture results become available, a switch to a more definitive therapy should be made to

reduce cost and toxicity while also preventing the emergence of resistant bacteria (Leekha *et al.*, 2011).

A multicentre study across sixty-seven ICUs in the US recorded that approximately 50% of all empiric antibiotics prescribed in critical patients were continued for at least three days without a confirmed infection (Thomas *et al.*, 2015). Another study in a paediatric ward of a public hospital in South Africa observed that 66.1% of antibiotic prescriptions were empiric, 18.4% were definitive, and 2.6% were prophylactic (Mabila *et al.*, 2016). Inappropriate empiric antibiotics were also reported in 43.5% and 60.85% of ICU patients in the public sector and private sectors, respectively, in South Africa (Paruk *et al.*, 2012).

In conclusion, the AMR crisis is an ongoing global challenge requiring continuous attention such as the implementation of AMS strategies and proper IPC practices. Information regarding the use of the antibiotic prescription chart as an AMS strategy is not well established. Thus, this study aimed to review antibiotic utilisation by investigating the impact of introducing an antibiotic prescription chart in an academic tertiary hospital.

CHAPTER 3

3. METHODOLOGY

3.1 Introduction

The study was a retrospective record review of antibiotic utilisation before and after a paper-based antibiotic prescription chart was introduced in two wards of an academic tertiary hospital and quantitative in nature. This chapter discusses the process of conducting this study and describes the study site, study design, sampling, study period, data collection method, ethical considerations and statistical analyses.

3.2 Study Site

The study was conducted in the adult infectious diseases and paediatric medical wards of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) located in Parktown, Johannesburg, Gauteng province. CMJAH is a 1088 bed academic hospital with over 4,000 staff members and is the principal teaching hospital for the University of the Witwatersrand, Faculty of Health Sciences (Gauteng Department of Health, 2009). It also functions as a referral hospital for several hospitals in its referral chain (Gauteng Department of Health, 2009).

The adult infectious diseases ward and paediatric medical ward consists of 24 beds each. The paediatric medical ward admits patients under the age of six with medical and non-infectious diagnosis. The adult infectious diseases ward has three isolation cubicles and admits mostly infectious diseases patients, including patients with complications of drug therapy. The wards were selected as non-critical wards with a high antibiotic consuming volume, where the antibiotic prescription chart was in use. Previous studies reviewing antibiotic utilisation in hospitals have been conducted in the ICU setting (Vitrat *et al.*, 2014).

3.3 Study Design and Sampling

This study was a descriptive, retrospective record review of data sourced from patient files, and paper-based antibiotic prescription charts of patients admitted into the selected wards during the study periods. All records of patients (male and female) admitted in the chosen wards throughout the study periods were included in the study. The exclusion criteria included:

- records of patients admitted outside both study periods,

- missing patient records, and
- records of patients who received other antimicrobials during the study periods.

3.4 Study Period

This study reviewed antibiotic utilisation records in two periods.

1. The first study period was between 1st August to 31st October 2016. This represented the period before the introduction of the antibiotic prescription chart at CMJAH.
2. The second study period was between 1st August to 31st October 2019 and represented the period following the introduction of the antibiotic prescription chart.

The same months were used in both study periods to avoid inconsistencies resulting from factors affecting disease patterns, such as change of season (Wesolowski *et al.*, 2017).

3.5 Data of Patients Collected

The variables described in Table 3.1 were collected for each study patient on a revised version of the CMJAH antibiotic prescription chart (Appendix 1) to anonymise patient data. Data from the pre-introduction study period were extracted from the patient's file, which includes medication charts, doctors' notes, laboratory flow charts and laboratory results sheet, which were all stored electronically. The antibiotic chart contained all information about patient demographics (age, weight, sex, allergies), antibiotics (dosage, frequency, duration, route of administration) and culture and sensitivity testing, and was used as the source of data for the post-antibiotic chart period. Data on the same variables were collected for each patient across both wards and periods of the study.

Hospital numbers of study participants were manually captured from the individual ward admissions book. The hospital numbers were then used to retrieve the necessary information for the study from scanned portable document format (PDF) files of patient records stored in a dedicated document management system on computers in the records department of the study site. The required data were manually recorded on the data collection tool and included demographic, clinical, laboratory and therapeutic data (Table 3.1) for each patient record included in the study. All the data captured were then transferred into a spreadsheet and coded.

Table 3.1: Data variables collected to review antibiotic utilisation before and after the introduction of an antibiotic prescription chart in CMJAH.

Data variable	**Description**
Unique patient study number	The researcher allocated this to ensure patient confidentiality
Ward	To identify the ward in which the study patient commenced antibiotic therapy
Demographics	Gender, age, weight
Diagnosis	Reason for patient admission
Infection source	To identify the infection source, as either hospital or community-acquired
Prescribed antibiotic	Antibiotics prescribed throughout the length of admission
Antibiotic dosage	Amount of antibiotics prescribed per dose
Antibiotic frequency	How often antibiotics were to be administered
Antibiotic duration	Length of antibiotic treatment
Basis of antibiotic prescribing	To determine if the prescribed antibiotic was prophylactic, empiric or definitive
Route of administration	Means of administering antibiotics for example oral, intravenous and intramuscular
Date of commencement of antibiotic	Date antibiotic therapy was started
End date of antibiotic therapy	Date antibiotic treatment was concluded
Length of hospital stay	To compare the length of admission of study participants as a study outcome measure
Duration of therapy	Number of days of antibiotic therapy
Timing of microbial cultures	To establish when culture samples were taken in comparison to the timing of antibiotics administered
Sensitivity results	To identify the causative organism of the infection and the susceptible and resistant antibiotics using drug-bug matching
Culture specimen type	To indicate the clinical specimens taken for culture tests such as urine, blood, sputum, stool or cerebrospinal fluid
Infection biomarkers	To determine if tests to identify infection biomarkers were done for example CRP and PCT tests

3.6 Statistical Analysis

The data variables collected using the data collection tool (Appendix 1) were captured on a Microsoft® Excel (2010) spreadsheet and analysed using Stata/IC 15.1 (StataCorp, USA). Patient characteristics and all outcome measures were quantitatively compared for both study periods and presented using descriptive analysis, as well as graphs and comparison tables. Categorical data such as gender, sensitivity testing and route of antibiotic administration were summarised as tables of frequencies (percentages) and illustrated with charts. Continuous data such as age, weight and length of hospital stay were reported as means (standard deviations) or median (inter-quartile range). Pearson's chi-square or Fisher's exact test was used to test associations between categorical variables. A *p*-value not exceeding 0.05 was regarded as significant.

3.7 Ethical Consideration

Ethical approval to conduct this study was granted by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190711 – Appendix 2) before the commencement of data collection. Hospital permission was also obtained from the Chief Executive Officer (CEO) of CMJAH (Appendix 3) and the heads of department of both wards (Appendices 4 and 5). The University of the Witwatersrand Protocol Assessment Committee approved the protocol to conduct the study (Appendix 6).

Unique study numbers were allocated to each study participant and stored in a password-protected document accessible to the principal investigator and supervisors alone. No patient personal information such as names and contact details were documented on the data collection tool. Patients' anonymity and confidentiality were maintained all through the study. Details of prescribers and other personnel involved in patient care were not captured or disclosed. No patient files were removed, copied or altered.

3.8 Data Reliability and Validity

3.8.1 Reliability

Reliability is a measure of consistently producing the same results under the same conditions repeatedly (Heale and Twycross, 2015). All data employed in this research was collected by the researcher alone from the patient records to reduce errors from multiple persons. No alteration was made to the data obtained which can be retrieved from the records department

for further research and yield the same results. Furthermore, unique study numbers were assigned to each patient record for easy tracing. The same variables were collected throughout the study and sorted before data analysis.

3.8.2 Validity

Heale and Twycross, (2015) define validity as the measure of precision employed in a quantitative study. Studies have employed the use of a similar data collection tool (Boyles *et al.*, 2013; Johnston *et al.*, 2018). Change in season may affect disease patterns. Given this, the researcher employed the same months across both study periods.

CHAPTER 4

4. RESULTS

4.1 Introduction

This chapter presents the results of data collected from both the adult and paediatric wards over both study periods, prior to the introduction of the antibiotic chart (2016) and after the introduction of the antibiotic chart (2019). Outcomes from both study periods were compared based on demographics, antibiotic utilisation, culture and sensitivity testing, the rationale for antibiotic prescribing and a review of the implementation of the antibiotic chart for patients who received antibiotics. Determinants of antibiotic prescribing were also evaluated using logistic regression methods.

A total of 366 admissions were documented in the adult ward; 200 in the pre-introduction period and 166 in the post-introduction period. Of these admissions, 93.50% (n=187) and 93.98% (n=156) of patient records had at least one antibiotic documented in the pre-introduction and post-introduction periods respectively.

In the paediatric ward, a total of 336 records of patients admitted within the study period were reviewed; 154 in the pre-introduction period, and 182 in the post-introduction period. Of this total, 76.62% (n=118) of the former and 64.83% (n=118) of the latter group received an antibiotic.

4.2 Patient Demographics

In the adult ward, 187 patient records were reviewed in the pre-introduction period and 156 in the post-introduction period (Table 4.1), while 118 patient records were each reviewed in both study periods in the paediatric ward (Table 4.2).

The mean patient age in the adult ward in the pre-introduction period recorded in this study was 37.77 ± 11.51 years and 41.08 ± 14.25 years in the post-introduction period with a statistically significant difference (p=0.0195) (Table 4.1). In the paediatric ward, the mean patient age in the pre-introduction period was 1.13 ± 2.35years, and 0.89 ± 1.41 years in the post-introduction period (Table 4.2), with no significant difference between patient age and study periods (p=0.2434). More male patients were recorded in both wards and over both periods of the study than females. However, the result of hypothesis testing using the

Pearson's chi-square test indicates there is no statistically significant difference between gender of participants and study periods in the adult ward (χ^2=0.3387; p=0.561) and paediatric ward (χ^2=2.2745; p=0.132).

The length of hospital stay was longer in both wards in the post-introduction period (adult ward = 10.45 days, paediatric ward = 8.18 days) as compared to the pre-introduction period (adult ward = 8.52 days, paediatric ward = 7.90 days). There was a statistically significant difference between the length of hospital stay across both study periods in the adult ward (p=0.0345) but no statistically significant difference in the paediatric ward (p=0.8234).

Table 4.1: Demographics in the adult ward

Demographics	**Pre-introduction**	**Post-introduction**	**P-value**
Number of patient records n (%)	187 (54.52)	156 (45.48)	
Age, years mean (SD)	37.77 (11.51)	41.08 (14.25)	0.0195
Gender; Male n (%)	96 (51.34)	85 (54.49)	0.561*
Gender; Female n (%)	91 (48.66)	71 (45.51)	
Weight, kg mean (SD)	58.03 (15.24)	57.70 (11.30)	
Length of hospital stay, mean days (SD)	8.52 (7.14)	10.45 (9.67)	0.0345

* Pearson's chi-square

Table 4.2: Demographics in the paediatric ward

Demographics	**Pre-introduction**	**Post-introduction**	**P-value**
Number of patient records n (%)	118 (50.00)	118 (50.00)	
Age, years mean (SD)	1.13 (2.35)	0.89 (1.41)	0.2434
Gender; Male n (%)	72 (61.02)	83 (70.34)	0.132*
Gender; Female n (%)	46 (38.98)	35 (29.66)	
Weight, kg mean (SD)	7.28 (5.61)	7.07 (4.81)	
Length of hospital stay, mean days (SD)	7.90 (7.32)	8.18 (11.48)	0.8234

* Pearson's chi-square

4.3 Diagnoses

A total of 179 diagnoses were recorded in this study (Appendix 7). These include primary diagnoses made on admission and those discovered after laboratory investigations. Tables 4.3 and 4.4 present the distribution of the common diagnoses in the adult and paediatric wards,

respectively. The most prevalent diagnoses reported in the adult ward in the pre-introduction period were tuberculosis (53.85%), meningitis (16.35%), pneumonia (11.06%) and sepsis (9.13%); while in the post-introduction period, there were mostly cases of pneumonia (34.27%), tuberculosis (29.58%), meningitis (16.43%), and intra-abdominal infections (6.57%) (Table 4.3).

Table 4.3: Common diagnosis of patients in the adult ward

Diagnosis	**Pre-introduction (N=208)**	**Post-introduction (N=213)**
Tuberculosis	112	63
Meningitis	34	35
Pneumonia	23	73
Sepsis	19	8
Intra-abdominal infection	11	14
Urinary tract infection	5	5
MDR Tuberculosis	3	2
Bacteraemia	1	11
Cellulitis	0	2

On the other hand, pneumonia and sepsis were the most frequent diagnosis in the paediatric ward across both study periods (Table 4.4). The source of infection was infrequently specified as either community or hospital-acquired in the pre-introduction period in both the adult (89.31%) and paediatric (0.00%) wards. The introduction of the antibiotic prescription chart in the post-introduction period resulted in a 50% and 51% reporting rate of infection sources in the adult and paediatric wards respectively.

Table 4.4: Common diagnosis of patients in the paediatric ward

Diagnosis	**Pre-introduction (N=83)**	**Post-introduction (N=74)**
Pneumonia	49	5
Sepsis	15	36
Intra-abdominal infection	9	7
Tuberculosis	5	1
UTI	4	12
Meningitis	1	13

4.4 Antibiotic Utilisation

4.4.1 Number of antibiotics prescribed

In both study periods, most patients admitted in the adult ward were on two antibiotics (pre-introduction period n=46, post-introduction period n=45), closely followed by those given one antibiotic (pre-introduction period n=42, post-introduction period n=37) (Figure 4.1). The mean number of antibiotics per patient in the adult ward was 2.92 ± 2.30 in the pre-introduction period and 2.54 ± 1.62 in the post-introduction period, with no statistically significant difference (p=0.3).

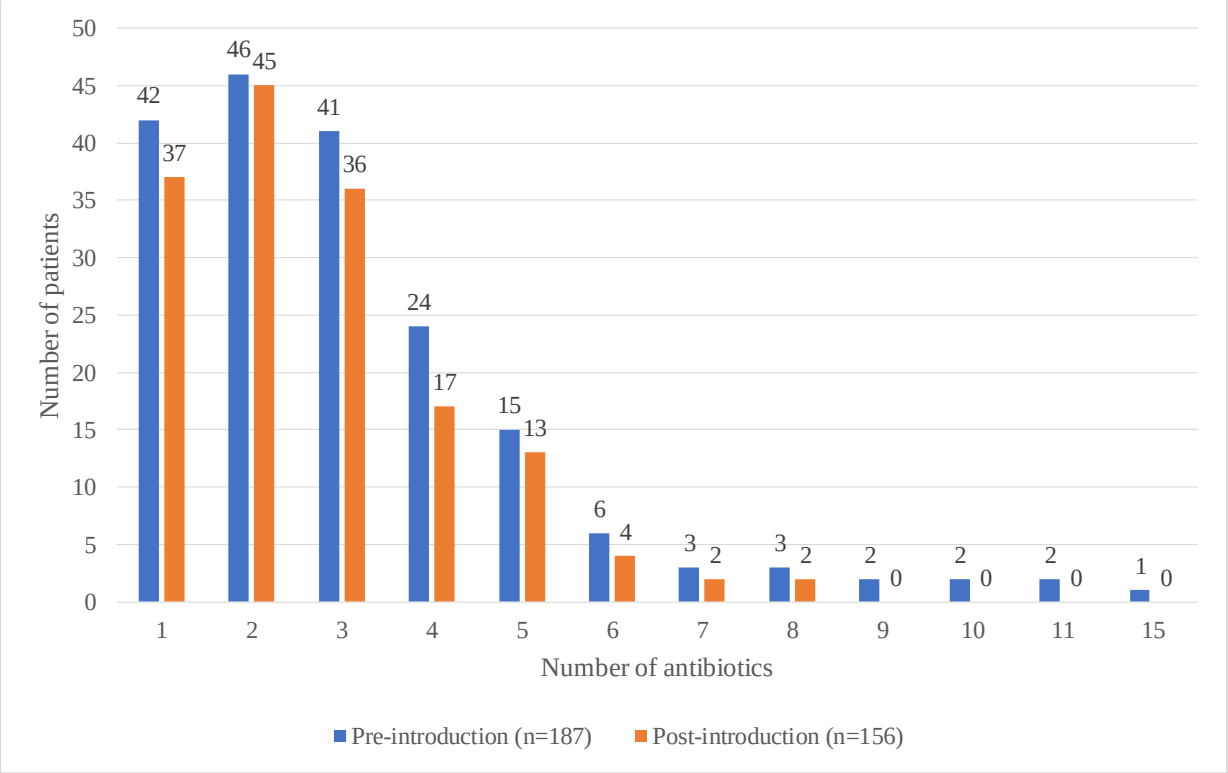

Figure 4.1: Number of antibiotics prescribed per patient in the adult ward

A total of eight antibiotics each were prescribed to two patients in the post-introduction period in the adult ward which was the maximum number of antibiotics prescribed per patient in that study period. Three patients received more than ten antibiotics in the pre-introduction period and are discussed as follows:

Patient X

Diagnosis: Nosocomial sepsis and disseminated tuberculosis

Length of stay: 42 days.

A total of 15 antibiotics were administered namely:

1. Metronidazole 400mg PO tds for 14 days
2. Ceftazidime 2g IV bd for 1 day
3. Linezolid 600mg IV bd for 12 days
4. Rifampicin/isoniazid/ pyrazinamide/ethambutol 4 tablets PO daily for 28 days
5. Sulfamethoxazole/trimethoprim 2 tablets PO daily for 29 days
6. Imipenem 500mg IV tds for 14 days
7. Ertapenem 1g IV daily for 10 days
8. Gentamycin 240mg IV daily for 9 days
9. Meropenem 1g IV tds for 1 day
10. Colistin 4.5mu IV bd for 4 days
11. Amoxicillin/clavulanic acid 1.2g IV qid for 2 days
12. Azithromycin 500mg PO daily for 1 day
13. Ceftriaxone 2g IV bd for 1 day
14. Vancomycin 1g IV stat on 2 occasions, 1.5g IV stat on 2 occasions and 2g IV stat on 1 occasion
15. Amikacin 1g IV stat on one occasion

The timeline of antibiotic administration for patient X is illustrated in Table 4.5.

Table 4.5: Timeline of antibiotic administration for patient X

Day*	**Antibiotics**	**Remarks***
D1-D7	Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/pyrazinamide/ethambutol Amoxicillin/clavulanic acid Ceftriaxone Azithromycin	Azithromycin administered on D1 only. Amoxicillin/clavulanic acid administered on D1 and D2. Ceftriaxone administered on D2 only.
D8-D14	Sulfamethoxazole/trimethoprim Imipenem Rifampicin/isoniazid/pyrazinamide/ethambutol	None
D15-D21	Sulfamethoxazole/trimethoprim Imipenem Rifampicin/isoniazid/pyrazinamide/ethambutol Ertapenem Amikacin stat dose Vancomycin stat dose	Ertapenem initiated on D21. Amikacin 1g stat on D21. Vancomycin 1g stat on D21.
D22-D28	Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/pyrazinamide/ethambutol Vancomycin stat doses Ertapenem	Vancomycin 1.5g stat on D22. Imipenem stopped on D22. Vancomycin 1.5g stat on D27. Vancomycin 1g stat on D28. Metronidazole initiated on D28.
D29-D35	Metronidazole Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/pyrazinamide/ethambutol Linezolid Gentamycin Vancomycin stat dose Ertapenem	Vancomycin 2g stat on D29. Sulfamethoxazole/trimethoprim stopped on D29. Rifampicin/isoniazid/pyrazinamide/ethambutol stopped on D29. Ertapenem stopped on D30.
D36-D42	Metronidazole Gentamycin Meropenem Ceftazidime Linezolid Colistin	Gentamycin stopped on D38. Meropenem administered on D38-D39. Colistin initiated on D39. Metronidazole stopped on D41. Ceftazidime administered on D41 only.

*D: day of hospital admission

The case summary of patient Y who was administered a total of 11 antibiotics in the pre-introduction period is described below, as well as a representation of the antibiotics administered in Table 4.6.

Patient Y

Diagnosis: Rifampicin-resistant tuberculosis and community-acquired pneumonia

Length of stay: 6 days.

A total of 11 antibiotics were administered namely:

1. Clindamycin 600mg PO qid for 5 days
2. Kanamycin 500mg IM daily for 2 days
3. Azithromycin 500mg PO daily for 3 days
4. Terizidone 250mg PO mane for 5 days
5. Ethionamide 250mg PO mane and 500mg nocte for 5 days
6. Pyrazinamide 2g PO daily for 5 days
7. Isoniazid 300mg PO daily for 4 days
8. Moxifloxacin 400mg PO daily for 4 days
9. Ethambutol 400mg PO daily for 4 days
10. Amoxicillin/clavulanic acid 1.2g IV qid for 6 days
11. Sulfamethoxazole/trimethoprim four ampoules IV qid for 6 days

The timeline of antibiotic administration for patient Y is illustrated in Table 4.6.

Table 4.6: Timeline of antibiotic administration for patient Y

Day*	**Antibiotics**	**Remarks***
D1-D6	Clindamycin	Clindamycin stopped on D5.
	Kanamycin	Kanamycin administered on D4-D5.
	Azithromycin	Azithromycin administered on D1-D3.
	Terizidone	Terizidone administered on D1-D5.
	Ethionamide	Ethionamide administered on D1-D5.
	Pyrazinamide	Pyrazinamide administered on D2-D5.
	Isoniazid	Isoniazid administered on D2-D5.
	Moxifloxacin	Moxifloxacin administered on D2-D5.
	Ethambutol	Ethambutol administered on D2-D5.
	Amoxicillin/clavulanic acid	
	Sulfamethoxazole/trimethoprim	

*D: day of hospital admission

The case summary of patient Z who was administered a total of 11 antibiotics in the pre-introduction period is described below, as well as a representation of the antibiotics administered in Table 4.7.

Patient Z

Diagnosis: Nosocomial sepsis and pulmonary tuberculosis

Length of stay: 42 days.

A total of 11 antibiotics were administered namely:

1. Sulfamethoxazole/trimethoprim two tablets PO daily for 35 days
2. Amoxicillin/clavulanic acid 600mg IV tds for 13 days
3. Piperacillin/tazobactam 4.5g IV tds for 1 day
4. Ceftriaxone 2g IV tds for 2 days
5. Rifampicin/isoniazid/pyrazinamide/ethambutol four tablets PO once daily on alternate days for 20 doses
6. Rifampicin/isoniazid two tablets PO once daily on alternate days for 13 doses
7. Ertapenem 1g IV daily for 9 days
8. Metronidazole 400mg PO tds for 11 days
9. Rifampicin 400mg PO nocte for 7 days
10. Vancomycin 12.5mg PO qid for 7 days
11. Colistin 4.5mu IV daily for 12 days

The timeline of antibiotic administration for patient Z is illustrated in Table 4.7

Table 4.7: Timeline of antibiotic administration for patient Z

Day*	**Antibiotics**	**Remarks**
D1-D7	Sulfamethoxazole/trimethoprim Amoxicillin/clavulanic acid Ceftriaxone Rifampicin/isoniazid/pyrazinamide/ethambutol Rifampicin/isoniazid	Sulfamethoxazole/trimethoprim initiated on D2. Amoxicillin/clavulanic acid not administered on D3. Ceftriaxone administered on D2-D3. Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D4 and D6. Rifampicin/isoniazid administered on D5 and D7.
D8-D14	Sulfamethoxazole/trimethoprim Amoxicillin/clavulanic acid Rifampicin/isoniazid/pyrazinamide/ethambutol Rifampicin/isoniazid	Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D8, D10, D12 and D14. Rifampicin/isoniazid administered on D9, D11 and D13.
D15-D21	Sulfamethoxazole/trimethoprim Piperacillin/tazobactam Ertapenem Rifampicin/isoniazid Rifampicin/isoniazid/pyrazinamide/ethambutol	Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D16, D18 and D20. Rifampicin/isoniazid administered on D15, D17, D19 and D21. Ertapenem initiated on D19.
D22-D28	Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/ pyrazinamide/ethambutol Rifampicin/isoniazid Colistin Rifampicin	Sulfamethoxazole/trimethoprim stopped on D22. Rifampicin/isoniazid administered on D23, D25 and D27. Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D22, D24, D26 and D28. Colistin initiated on D23. Rifampicin initiated on D28.
D29-D35	Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/pyrazinamide/ethambutol Rifampicin Vancomycin Metronidazole Colistin	Vancomycin initiated on D32. Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D30, D32 and D34. Colistin stopped on D34. Rifampicin stopped on D34.

Day*	Antibiotics	Remarks
D36-42	Sulfamethoxazole/trimethoprim Rifampicin/isoniazid/pyrazinamide/ethambutol Metronidazole Vancomycin	Rifampicin/isoniazid/pyrazinamide/ethambutol administered on D36, D38, D40 and D42. Metronidazole stopped on D39. Vancomycin stopped on D38.

*D: day of hospital admission

Three carbapenems were administered to patient X during the length of admission, with imipenem and meropenem administered simultaneously on day 21 of admission. Furthermore, rifampicin alongside rifampicin/isoniazid/pyrazinamide/ethambutol fixed-dose combination was administered to patient X on four occasions. Patient Z was administered ceftriaxone alongside amoxicillin/clavulanic acid on day 2 of admission. These scenarios suggest duplicate antibiotic coverage.

In the paediatric ward, 44.07% and 39.83% of patients on antibiotics in the pre-introduction and post-introduction periods respectively were administered one antibiotic, followed by those receiving two antibiotics (Figure 4.2). Patient records in the paediatric ward documented an average of 1.60 ± 1.52 antibiotics prescribed in the pre-antibiotic period and 1.31 ± 1.41 in the post-introduction period with no statistically significant difference (p=0.054).

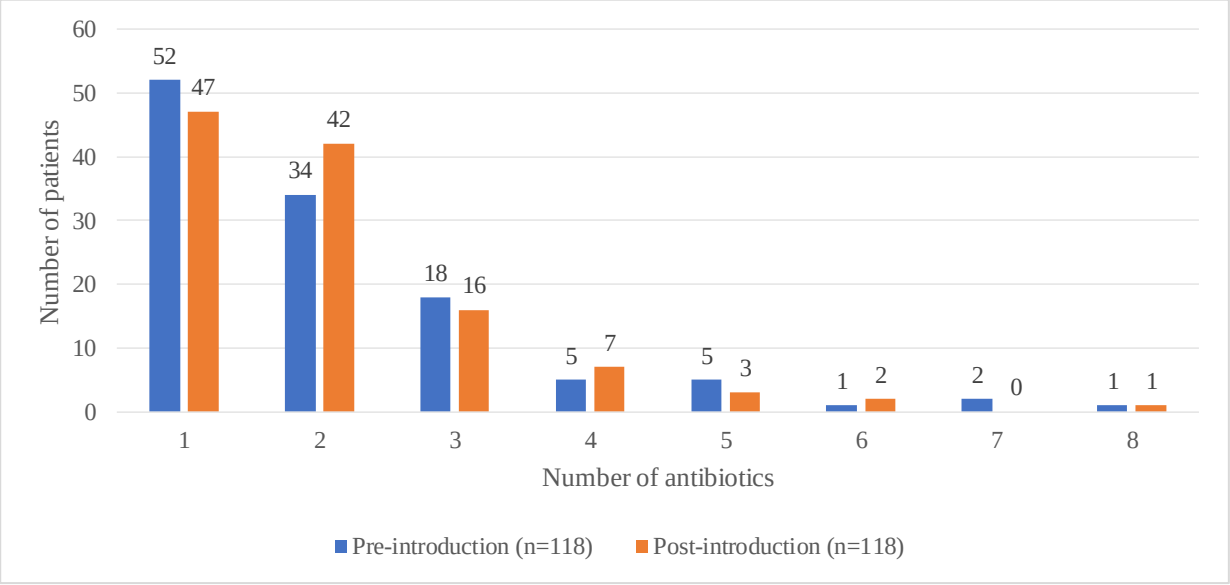

Figure 4.2: Number of antibiotics prescribed per patient in the paediatric ward

4.4.2 Duration of antibiotic therapy

The distribution of patients in the adult and paediatric wards are depicted in Tables 4.8 and 4.9 respectively, according to the number of antibiotic days. The classification of the duration of antibiotic therapy was adapted from Amaha *et al.* (2018).

In the adult ward, antibiotic regimens of one to seven days were frequent in both the pre-introduction period (60.96%) and post-introduction period (55.13%) (Table 4.8). Within the proportion of patients on antibiotic therapy for 15 days and above, a total of 73.91% of patients in the pre-introduction period and 42.31% of patients in the post-introduction period were on antituberculosis agents which require an extended period of therapy. A decrease in the average duration of antibiotic therapy from 6.47 ± 5.50 days in the pre-introduction period to 6.05 ± 4.77 days in the post-introduction period in the adult ward was recorded when patients on antituberculosis therapy and HIV prophylaxis with sulfamethoxazole/trimethoprim combination were excluded.

Table 4.8: Duration of antibiotic therapy in the adult ward

Duration of antibiotic therapy	**Pre-introduction period N=187 n (%)**	**Post-introduction period N=156 n (%)**
1–7 days	114 (60.96)	86 (55.13)
7–14 days	50 (26.74)	44 (28.21)
15–20 days	15 (8.02)	12 (7.69)
> 21 days	8 (4.28)	14 (8.97)

The paediatric ward had 78.81% and 79.66% of patients on antibiotics for one to seven days in the pre-introduction and post-introduction periods respectively (Table 4.9). A total of 94.07% and 93.22% antibiotic therapies were completed within 14 days in the pre-introduction and post-introduction periods respectively. The average duration of antibiotic therapy was 5.59 ± 3.78 days and 5.46 ± 4.25 days in the pre-introduction and post-introduction periods respectively on the exclusion of patients on antituberculosis therapy. Patients with longer antibiotic days were being managed for chronic and severe conditions including pulmonary tuberculosis, nosocomial pneumonia, recurrent sepsis and meningitis which may require longer periods of antibiotic therapy.

Table 4.9: Total duration of antibiotic therapy in the paediatric ward

Duration of antibiotic therapy	Pre-introduction period N=118 n (%)	Post-introduction period N=118 n (%)
1–7 days	93 (78.81)	94 (79.66)
7–14 days	18 (15.25)	16 (13.56)
15–20 days	3 (2.55)	4 (3.39)
> 21 days	4 (3.39)	4 (3.39)

4.4.3 Antibiotics prescribed

The recorded antibiotics prescribed in the adult ward were similar in both study periods as there was no change in the hospital's formulary in the interim. These include rifampicin/isoniazid/pyrazinamide/ethambutol (pre-introduction: 17.01%, post-introduction: 19.27%), amoxicillin/clavulanic acid (pre-introduction: 16.32%, post-introduction: 19.96%) sulfamethoxazole/trimethoprim (pre-introduction: 14.23%, post-introduction: 10.55%), and ceftriaxone (pre-introduction: 7.99%, post-introduction: 9.86%) (Table 4.10). Rifampicin/isoniazid/pyrazinamide/ethambutol, rifampicin/isoniazid, amoxicillin/clavulanic acid, sulfamethoxazole/trimethoprim and piperacillin/tazobactam fixed dose combination are reported as single antibiotics.

Table 4.10: Antibiotics prescribed in both study periods in the adult ward

Antibiotic	Antibiotics prescribed in the pre-introduction period n (%)	Antibiotics prescribed in the post-introduction period n (%)
Rifampicin/isoniazid/ pyrazinamide/ethambutol	98 (17.01)	84 (19.27)
Amoxicillin/clavulanic acid	94 (16.32)	87 (19.96)
Sulfamethoxazole/trimethoprim	82 (14.23)	46 (10.55)
Ceftriaxone	46 (7.99)	43 (9.86)
Metronidazole	30 (5.21)	5 (1.15)
Azithromycin	30 (5.21)	50 (11.46)
Piperacillin/tazobactam	24 (4.17)	11 (2.52)
Rifampicin/isoniazid	23 (3.99)	18 (4.13)
Ethambutol	23 (3.99)	14 (3.21)
Moxifloxacin	22 (3.82)	9 (2.06)

Antibiotic	**Antibiotics prescribed in the pre-introduction period n (%)**	**Antibiotics prescribed in the post-introduction period n (%)**
Isoniazid	15 (2.60)	7 (1.61)
Rifampicin	11 (1.91)	2 (0.46)
Cefotaxime	10 (1.74)	0 (0.00)
Kanamycin	9 (1.56)	0 (0.00)
Ertapenem	8 (1.39)	4 (0.92)
Ethionamide	7 (1.22)	1 (0.23)
Vancomycin	6 (1.04)	4 (0.92)
Pyrazinamide	6 (1.04)	6 (1.38)
Terizidone	6 (1.04)	0 (0.00)
Ciprofloxacin	4 (0.69)	0 (0.00)
Clindamycin	3 (0.52)	0 (0.00)
Cloxacillin	3 (0.52)	1 (0.23)
Imipenem	3 (0.52)	1 (0.23)
Colistin	3 (0.52)	0 (0.00)
Amikacin	2 (0.35)	5 (1.15)
Ceftazidime	2 (0.35)	0 (0.00)
Linezolid	2 (0.35)	5 (1.15)
Doxycycline	2 (0.35)	2 (0.46)
Meropenem	1 (0.17)	3 (0.69)
Gentamycin	1 (0.17)	0 (0.00)
Cefazolin	0 (0.00)	3 (0.69)
Amoxicillin	0 (0.00)	1 (0.23)
Ampicillin	0 (0.00)	3 (0.69)
Clofazimine	0 (0.00)	6 (1.38)
Clarithromycin	0 (0.00)	1 (0.23)
Levofloxacin	0 (0.00)	7 (1.61)
Flucloxacillin	0 (0.00)	1 (0.23)
Bedaquiline	0 (0.00)	5 (1.15)
Tigecycline	0 (0.00)	1 (0.23)
Total	**576 (100.00)**	**436 (100.00)**

The most commonly administered antibiotics in the paediatric ward were also similar in both study periods, and include ampicillin (pre-introduction: 18.70%, post-introduction: 17.70%), gentamycin (pre-introduction: 14.23%, post-introduction: 13.17%), and cefotaxime (pre-introduction: 13.01%, post-introduction: 5.76%) (Table 4.11).

Table 4.11: Antibiotics prescribed in both study periods in the paediatric ward

Antibiotic	**Antibiotics prescribed in the pre-introduction period n (%)**	**Antibiotics prescribed in the post-introduction period n (%)**
Ampicillin	46 (18.70)	43 (17.70)
Gentamycin	35 (14.23)	32 (13.17)
Cefotaxime	32 (13.01)	14 (5.76)
Amoxicillin/Clavulanic acid	29 (11.79)	36 (14.82)
Amoxicillin	14 (5.69)	9 (3.70)
Ceftriaxone	14 (5.69)	16 (6.58)
Amikacin	11 (4.47)	17 (7.00)
Piperacillin/Tazobactam	10 (4.07)	19 (7.82)
Sulfamethoxazole/Trimethoprim	9 (3.66)	5 (2.06)
Azithromycin	8 (3.25)	7 (2.88)
Cloxacillin	6 (2.44)	2 (0.82)
Pyrazinamide	6 (2.44)	3 (1.23)
Rifampicin/Isoniazid	6 (2.44)	3 (1.23)
Vancomycin	4 (1.63)	5 (2.06)
Meropenem	4 (1.63)	5 (2.06)
Isoniazid	3 (1.22)	0 (0.00)
Cephalexin	2 (0.81)	0 (0.00)
Ethambutol	2 (0.81)	2 (0.82)
Flucloxacillin	2 (0.81)	0 (0.00)
Ertapenem	1 (0.41)	0 (0.00)
Rifampicin	1 (0.41)	0 (0.00)
Ceftazidime	1 (0.41)	12 (4.94)
Cefazolin	0 (0.00)	7 (2.88)
Metronidazole	0 (0.00)	2 (0.82)
Clindamycin	0 (0.00)	1 (0.41)

Antibiotic	Antibiotics prescribed in the pre-introduction period n (%)	Antibiotics prescribed in the post-introduction period n (%)
Chloramphenicol ointment	0 (0.00)	3 (1.23)
Total	**246 (100.00)**	**243 (100.00)**

4.4.4 Route of administration

Overall, both oral and parenteral antibiotics were concurrently administered to patients in the adult ward in both study periods (pre-introduction period: 61.50%, post-introduction period: 60.26%) (Table 4.12).

Table 4.12: Antibiotic routes of administration in the adult ward

Route of administration	Pre-introduction n (%)	Post-introduction n (%)
Oral only	45 (24.06)	37 (23.72)
Parenteral only	27 (14.44)	25 (16.02)
Oral and parenteral	115 (61.50)	94 (60.26)
Total	**187 (100.00)**	**156 (100.00)**

On the other hand, in the paediatric ward, the preferred route of administration for antibiotics was the parenteral route in both the pre-introduction (54.24%) and post-introduction (65.26%) periods (Table 4.13). This could be due to the commonly prescribed antibiotics in the paediatric ward namely ampicillin, gentamycin and cefotaxime being only available in the parenteral form in the study facility.

Table 4.13: Antibiotic routes of administration in the paediatric ward

Route of administration	Pre-introduction n (%)	Post-introduction n (%)
Oral only	15 (12.71)	19 (16.10)
Parenteral only	64 (54.24)	77 (65.26)
Oral and parenteral	39 (33.05)	22 (18.64)
Total	**118 (100.00)**	**118 (100.00)**

4.4.5 Rationale for antibiotic prescribing

The rationale for prescribing antibiotics was occasionally (adult ward: 10.16%, paediatric ward: 0.00%) indicated in patient's records (doctors' notes or discharge summary) of both wards in

the pre-introduction period, as it was not required in the previously used medication prescription chart which contained all prescribed medicines including antibiotics. In the post-introduction period antibiotics were commonly prescribed empirically on the antibiotic chart in the adult (20.51%) and paediatric wards (41.53%), followed by definitive therapy (Tables 4.14 and 4.15). An improvement in the documentation of rationales for antibiotic prescribing from 10.16% in the pre-introduction period to 33.33% in the post-introduction period in the adult ward and from 0% in the pre-introduction period to 50.87% in the post-introduction period in the paediatric ward was observed in this study.

Table 4.14: Rationale for antibiotic prescribing in the adult ward

Rationale for antibiotic prescribing*	**Pre-introduction period N=187 n (%)**	**Post-introduction period N=156 n (%)**
E	19 (10.16)	32 (20.51)
D	0 (0.00)	15 (9.62)
ED	0 (0.00)	4 (2.56)
P	0 (0.00)	1 (0.64)
Not documented	168 (89.84)	104 (66.67)

*P: prophylactic; ED: empiric therapy subsequently switched to definitive; D: definitive; E: empiric

Table 4.15: Record of rationale for antibiotic prescribing in the paediatric ward

Rationale for antibiotic prescribing*	**Pre-introduction period N=118 n (%)**	**Post-introduction period N=118 n (%)**
E	0 (0.00)	49 (41.53)
ED	0 (0.00)	5 (4.24)
D	0 (0.00)	4 (3.40)
P	0 (0.00)	2 (1.70)
Not documented	118 (100.00)	58 (49.13)

*P: prophylactic; ED: empiric therapy subsequently switched to definitive; D: definitive; E: empiric

4.5 Culture and Sensitivity Testing

4.5.1 Frequency of culture testing

For those patients who received antibiotics, microbial cultures were requested in 51.34% (n=96) of patients in the pre-introduction period. This increased slightly to 56.41% (n=88) in the post-introduction period in the adult ward (Table 4.16), while 34.22% and 19.87% of cultures had been done in a previous ward or facility in the pre-introduction and post-introduction periods respectively. The percentage of undocumented cultures in the adult ward increased by 9.28% in the post-introduction period.

In the paediatric ward, the proportion of cultures requested in the pre-introduction period was 74.58% and this increased by 6.78% in the post-introduction period (Table 4.17). The number of undocumented culture tests decreased from 21.18% (n=25) in the pre-introduction period to 15.25% (n=18) in the post-introduction period.

Table 4.16: Frequency of culture and sensitivity testing in the adult ward

Culture and sensitivity	**Pre-introduction n (%)**	**Post-introduction n (%)**
Sent in ward	96 (51.34)	88 (56.41)
Previously tested in a different ward or facility	64 (34.22)	31 (19.87)
No record of test	27 (14.44)	37 (23.72)

Table 4.17: Frequency of culture and sensitivity testing in the paediatric ward

Culture and sensitivity	**Pre-introduction n (%)**	**Post-introduction n (%)**
Sent in ward	88 (74.58)	96 (81.36)
Previously tested in a different ward or facility	5 (4.24)	4 (3.39)
No record of test	25 (21.18)	18 (15.25)

4.5.2 Culture and sensitivity results with isolated pathogens

The pathogens isolated, the sample tested and the sensitivity of the isolated pathogen to the antibiotic are depicted in Tables 4.18 and 4.19. In the adult ward, *Haemophilus influenzae* was the most isolated pathogen in the pre-introduction period (n=6) and Coagulase-negative *Staphylococcus* in the post-introduction period (n=5) (Table 4.18). *Acinetobacter baumannii* was isolated in three cultures in the pre-introduction phase in the adult ward, and once each in

both study periods in the paediatric ward. On three occasions, resistance to colistin was recorded; one in the pre-introduction period in the adult ward and one time each in both study periods in the paediatric ward. A case of rifampicin-resistant *Mycobacterium tuberculosis* was also observed in the adult ward in the pre-introduction period. No pathogen was isolated in 75, and 69 samples in the pre-introduction and post-introduction periods in the adult ward. This may have resulted from prior initiation of an antimicrobial therapy before obtaining culture samples from the patients as well as patients on prior anti-tuberculosis medication or prophylaxis with Sulfamethoxazole/trimethoprim. Of these, antibiotics were discontinued in two patients each in both study periods in the adult ward.

Coagulase-negative *Staphylococcus* (n=5) was the most frequently cultured pathogen in the paediatric ward in the pre-introduction period, and *Klebsiella pneumonia* (n=8) in the post-introduction period respectively (Table 4.19). In the paediatric ward, 97.26% and 100% of patients whose microbial cultures presented no growth were continued on their prescribed antibiotic in the pre-introduction and post-introduction periods respectively, which may have been empiric.

Table 4.18: Isolated pathogens and sensitivities in the adult ward

		Pre-introduction period N=111			Post-introduction period N=94		
Isolated pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Haemophilus influenzae	Blood Sputum	6	Tetracycline Sulfamethoxazole/trimethoprim Ampicillin Amoxicillin	Ampicillin Cefuroxime Chloramphenicol Amoxicillin Tetracycline Meropenem			
Enterococcus faecium	Pleural fluid CSF Blood	4	Ampicillin Ciprofloxacin Erythromycin Moxifloxacin Tetracycline Clindamycin	Vancomycin Tigecycline Linezolid Gentamycin Sulfamethoxazole/trimethoprim			
Acinetobacter baumannii	Blood Sputum Urine CSF IV catheter tip	3	Amoxicillin/clavulanic acid Cefotaxime Cefoxitin Ceftazidime Cefuroxime Imipenem Amikacin	Colistin Tigecycline			
Gram-positive cocci	Sputum Pus swab	3	-	-	2	-	-
Escherichia coli	Blood Urine	2	Ciprofloxacin Amikacin Sulfamethoxazole/trimethoprim Amoxicillin/clavulanic acid Cefazolin	Amoxicillin/clavulanic acid Amikacin Fosfomycin Ertapenem Ciprofloxacin	3	Amoxicillin/clavulanic acid Cefazolin Cefuroxime Gentamycin Piperacillin/tazobactam Sulfamethoxazole/trimethoprim	Amikacin Ceftriaxone Cefotaxime Ceftazidime Cefoxitin Ciprofloxacin Imipenem

		Pre-introduction period N=111			Post-introduction period N=94		
Isolated pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Mycobacterium tuberculosis	Sputum	2	Rifampicin	Rifampicin	2	-	Rifampicin
Enterococcus faecalis	Blood Urine	2	Clindamycin Tetracycline	Ampicillin Vancomycin Linezolid Tigecycline Moxifloxacin Gentamycin Sulfamethoxazole/trimethoprim			
Coagulase-negative *staphylococcus*	Blood	2	Ampicillin Sulfamethoxazole/trimethoprim Rifampicin	Ciprofloxacin Azithromycin Gentamycin Linezolid Vancomycin Sulfamethoxazole/trimethoprim	5	Sulfamethoxazole/trimethoprim Cloxacillin Azithromycin Penicillin	Ciprofloxacin Clindamycin Cloxacillin Gentamycin Linezolid Vancomycin
Clostridium difficile	Stool	2	-	-			
Staphylococcus aureus	Urine Sputum	2	Clindamycin Ampicillin Ciprofloxacin Tetracycline Rifampicin	Cloxacillin Ciprofloxacin Tigecycline Linezolid Gentamycin	3	Sulfamethoxazole/trimethoprim	Cloxacillin Ciprofloxacin Clindamycin Azithromycin Gentamycin Linezolid Vancomycin Moxifloxacin
Cryptococcus neoformans	Blood	1	-	-			
Prevotella oralis	Pus swab	1	-	Penicillin Clindamycin			

		Pre-introduction period N=111			Post-introduction period N=94		
Isolated pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Salmonella group D	Blood	1	-	Ceftriaxone Ciprofloxacin Colistin Ertapenem Gentamycin Piperacillin/tazobactam			
Gram-negative bacteria	Blood CSF	1	Colistin Nitrofurantoin	Ceftazidime Ceftriaxone Ciprofloxacin Meropenem Sulfamethoxazole/trimethoprim Piperacillin/tazobactam			
Burkholderia cepacia	Urine	1	Amikacin Amoxicillin Cefoxitin Colistin Gentamycin Imipenem Piperacillin/tazobactam	Ceftriaxone Tigecycline Ceftazidime Meropenem Sulfamethoxazole/trimethoprim			
Staphylococcus haemolyticus	Blood	1	Ciprofloxacin Gentamycin Ampicillin Tetracycline Sulfamethoxazole/trimethoprim	Vancomycin Clindamycin Azithromycin Moxifloxacin Linezolid			
Enterobacter cloacae	Sputum Pus swab	1	Amoxicillin/clavulanic acid Ampicillin Cefoxitin	Ertapenem Imipenem Cefotaxime Ceftriaxone Gentamycin	2	Amoxicillin/clavulanic acid Cefoxitin Sulfamethoxazole/trimethoprim	Amikacin Ceftriaxone Ceftazidime Ciprofloxacin Ertapenem

		Pre-introduction period N=111			Post-introduction period N=94		
Isolated pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Viridans streptococcus	Blood	1	-	Clindamycin Erythromycin Linezolid Cefotaxime Vancomycin Sulfamethoxazole/trimethoprim			
Klebsiella pneumoniae	Urine Sputum				3	Amoxicillin/clavulanic acid Cefepime Ceftriaxone Cefotaxime Cefoxitin Ceftazidime Cefuroxime Ciprofloxacin Gentamycin Meropenem Piperacillin/tazobactam Sulfamethoxazole/trimethoprim	Amikacin Imipenem Cloxacillin linezolid Vancomycin
Streptococcus pneumoniae	Blood CSF				3	-	Amoxicillin/clavulanic acid Ceftriaxone Azithromycin Linezolid Moxifloxacin Vancomycin
Staphylococcus Hominis	Blood				1	Clindamycin Azithromycin Penicillin Rifampicin Tetracycline	Cloxacillin Linezolid Moxifloxacin Vancomycin Sulfamethoxazole/trimethoprim

		Pre-introduction period N=111			Post-introduction period N=94		
Isolated pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Streptococcus salivarius	Blood				1	-	Cefotaxime Ceftriaxone Erythromycin Ampicillin Vancomycin Linezolid
No pathogen isolated	Blood Urine Sputum	75	-	-	69	-	-

*-: None

Table 4.19: Isolated pathogens and sensitivities in the paediatric ward

		Pre-introduction period N=99			Post-introduction period N=120		
Pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Coagulase-negative *staphylococcus*	Blood	5	Tetracycline Cloxacillin Erythromycin Penicillin Rifampicin Sulfamethoxazole/trimethoprim Gentamycin	Cloxacillin Ciprofloxacin Clindamycin Erythromycin Gentamycin Linezolid Vancomycin	2	Ampicillin Sulfamethoxazole/trimethoprim	Cefazolin Ciprofloxacin Erythromycin Gentamycin Linezolid Rifampicin Vancomycin
Klebsiella pneumoniae	Urine Blood	5	Amoxicillin/clavulanic acid Ampicillin Cefotaxime Ceftriaxone Cefepime Gentamycin Sulfamethoxazole/trimethoprim	Amikacin Ertapenem Imipenem Ciprofloxacin Cefuroxime Imipenem Ertapenem Colistin	8	Ampicillin Ciprofloxacin Gentamycin	Amikacin Ertapenem Ceftazidime Fosfomycin Cefotaxime Sulfamethoxazole/trimethoprim Meropenem Cefoxitin
Staphylococcus aureus	Pleural fluid Blood Sputum Pus swab	4	Penicillin	Cloxacillin Ciprofloxacin Moxifloxacin Rifampicin Tigecycline Vancomycin	5	Ciprofloxacin Gentamycin Moxifloxacin Penicillin Tetracycline Sulfamethoxazole/trimethoprim	Linezolid Cefazolin Clindamycin Cloxacillin Erythromycin Vancomycin Rifampicin Tigecycline
Gram-positive cocci	Pus swab Blood Sputum	2	-	Ampicillin	4	-	-

		Pre-introduction period N=99			Post-introduction period N=120		
Pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Escherichia coli	Urine Pus swab Blood	2	Sulfamethoxazole/trimethoprim Ampicillin	Amoxicillin/clavulanic acid Ciprofloxacin Amoxicillin Gentamycin	7	Ampicillin Amoxicillin/clavulanic acid Cefotaxime Ceftriaxone Cefuroxime	Ampicillin Gentamycin Piperacillin/tazobactam Ertapenem Nitrofurantoin Meropenem Amoxicillin/clavulanic acid Amikacin Ceftazidime
Staphylococcus hominis	Blood	2	Clindamycin Cloxacillin Erythromycin Penicillin Sulfamethoxazole/trimethoprim	Gentamycin Moxifloxacin Tetracycline Tigecycline Vancomycin			
Acinetobacter baumannii	Sputum	1	Amoxicillin/clavulanic acid Ampicillin Cefotaxime Cefoxitin Ceftriaxone Cefuroxime	Ciprofloxacin Cefepime Amikacin Ceftazidime Colistin Gentamycin Imipenem Sulfamethoxazole/trimethoprim Piperacillin/tazobactam	1	Cefotaxime Ceftriaxone	Ceftazidime Colistin Gentamycin Imipenem Piperacillin/tazobactam Tigecycline
Enterococcus faecium	Blood	1	Ciprofloxacin Clindamycin Azithromycin Moxifloxacin Penicillin	Vancomycin Linezolid Tigecycline			

		Pre-introduction period N=99			Post-introduction period N=120		
Pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Enterobacter aerogenes	Sputum	1	Amoxicillin/clavulanic acid Ampicillin	Ciprofloxacin Cefepime Amikacin Cefotaxime Ceftazidime Cefuroxime Colistin Ertapenem Gentamycin Sulfamethoxazole/trimethoprim Piperacillin/tazobactam			
Pseudomonas aeruginosa	Pus swab	1	Amoxicillin/clavulanic acid Ampicillin Ceftriaxone Cefuroxime	Amikacin Ceftazidime Ciprofloxacin Colistin Gentamycin			
Staphylococcus haemolyticus	Blood	1	Cloxacillin Gentamycin Penicillin Sulfamethoxazole/trimethoprim	Ciprofloxacin Tetracycline Tigecycline Vancomycin			
Klebsiella oxytoca	Urine				2	Ampicillin Cefotaxime Ceftazidime Cefuroxime Ciprofloxacin Gentamycin Ceftriaxone Sulfamethoxazole/trimethoprim	Piperacillin/tazobactam Nitrofurantoin Cefoxitin Ertapenem Imipenem

		Pre-introduction period N=99			Post-introduction period N=120		
Pathogen	**Sample tested**	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***	**Frequency of isolation**	**Antibiotics to which organism was resistant***	**Antibiotics to which organism was sensitive***
Staphylococcus epidermidis	Blood				4	Ciprofloxacin Erythromycin Penicillin Sulfamethoxazole/trimethoprim	Linezolid Rifampicin Vancomycin
Streptococcus species	Blood	1	-	Cefotaxime Ceftriaxone Clindamycin Erythromycin Linezolid Penicillin Vancomycin	1	Ceftriaxone Penicillin	Clindamycin Erythromycin Linezolid Vancomycin
Proteus mirabilis	Urine				1	Tigecycline	Ampicillin Amikacin Amoxicillin/clavulanic acid Ceftriaxone Ceftazidime Cefuroxime Ciprofloxacin Ertapenem
Streptococcus pneumoniae	Blood CSF				1	-	Ceftriaxone Amoxicillin/clavulanic acid
No pathogen isolated	CSF Sputum Blood	73	-	-	79	-	-

*-: None

4.6 Infection Markers

The CRP tests were routinely done for most patients in both wards and study periods (Tables 4.20 and 4.21). PCT was performed in 47 (25.13%) patients in the adult ward in the pre-introduction period and 26 (16.67%) patients in the post-introduction period. PCT was also performed in 10 (8.47%) patients in the paediatric ward in the pre-introduction period and eight (6.78%) patients in the post-introduction period. There was no statistically significant difference in the frequency of CRP testing between both study periods in the adult (p=0.432) and paediatric (p=0.139) wards. However, the proportion of PCT tests conducted was significantly greater in the pre-introduction period in the adult ward (p=0.039), however, no significant difference in both study periods in the paediatric ward (p=0.423). The antibiotic prescription chart did not contain a data field where results for infection markers could be recorded.

Table 4.20: Infection markers in the adult ward

Infection markers	Pre-introduction (N = 187)	Post-introduction (N = 156)
CRP	167	135
PCT	47	26

Table 4.21: Infection markers in the paediatric ward

Infection markers	Pre-introduction (N=118)	Post-introduction (N=118)
CRP	102	109
PCT	10	8

4.7 Antibiotic Prescription Chart Audit in the Post-Introduction Period

4.7.1 Record of patient demographics

In the adult ward, seven patients (4.49%) had their ages documented on the antibiotic prescription chart, while 12 (7.69%) and 14 (8.97%) patients respectively had their weights and allergies documented in the antibiotic chart in the post-introduction period. In the paediatric ward, 69 (58.47%) and 51 (43.22%) of patients respectively had weight and allergies documented on the antibiotic prescription charts, with no ages recorded (Table 4.22). There was no data field allocated for the documentation of gender in the antibiotic prescription chart.

Table 4.22: Patient demographics recorded on the antibiotic chart in the post-introduction period

Demographics fields	Adult ward (N=156)	Paediatric ward (N=118)
Age	7	0
Weight	12	69
Allergies	14	51

4.7.2 Record of renal function test

GFR and Cr/Cl test values were documented in the antibiotic charts of 48 adults (30.77%) and three paediatric (2.54%) patients in the post-introduction period (Figure 4.3).

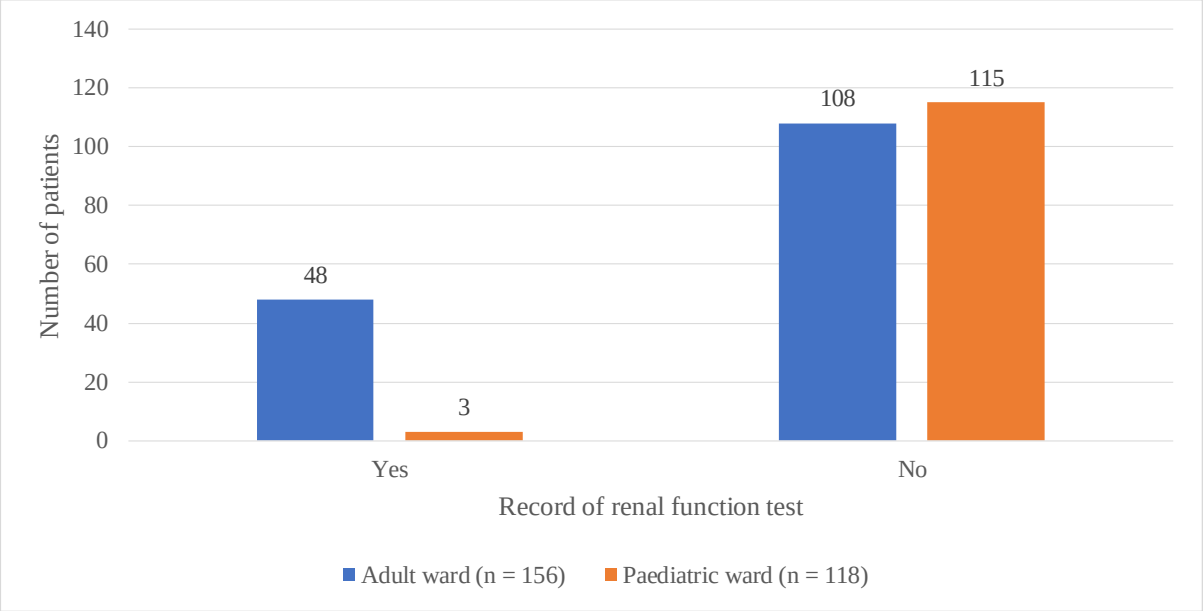

Figure 4.3: Record of renal function test in the post-introduction period

4.7.3 Patient diagnosis, infection source and timing of culture

4.7.3.1 Record of diagnoses

In the adult ward, 66.67% (n=104) of diagnoses were recorded on the antibiotic chart and 78.81% (n=93) in the paediatric ward (Figure 4.4). Of the 104 diagnoses recorded on the antibiotic chart in the adult ward and 93 in the paediatric ward, 16.03% and 19.49% of the antibiotic charts had a different diagnosis from those documented in the patients' hospital records, respectively.

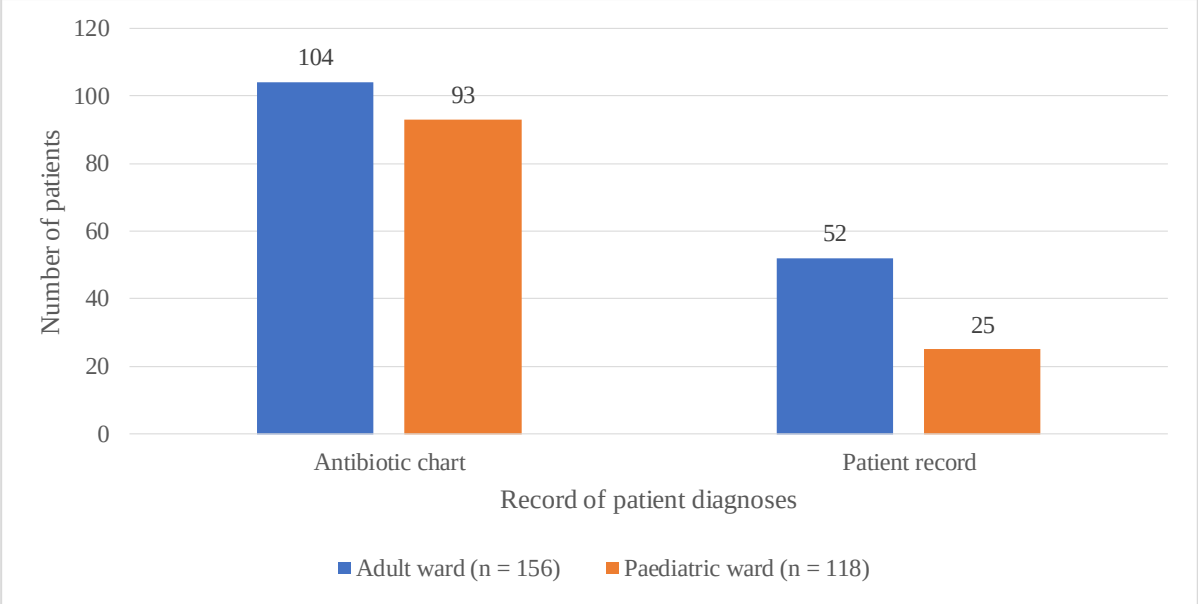

Figure 4.4: Record of patient diagnoses

4.7.3.2 Record of infection source

Sources of infection were classified as either community or hospital-acquired. Sources of infection were predominantly recorded in both wards on the antibiotic prescription chart, as prescribers were required to include this information. In the post-introduction period, most infections were community-acquired in the adult ward (42.95%) and paediatric ward (42.37%), followed by a few cases of hospital-acquired infections (Table 4.23). There was no record for a source of infection in 48.72% of antibiotic prescription charts in the adult ward, and 47.46% of antibiotic prescription charts in the paediatric ward.

Table 4.23: Record of infection source on the antibiotic prescription chart

Infection source	**Adult ward (N=156)** **n (%)**	**Paediatric ward (N=118)** **n (%)**
Not recorded	76 (48.72)	56 (47.46)
Community	67 (42.95)	50 (42.37)
Hospital	9 (5.77)	11 (9.32)
Both	4 (2.56)	1 (0.85)

4.7.3.3 Record of timing of culture

In the post-introduction period, cultures requested in the ward were noted to have been sent before initiating antibiotic therapy for 56.82% (n = 50) of patients admitted in the adult ward and 59.38% (n = 57) in the paediatric ward (Table 4.24). The timings of cultures requested in

the ward were not documented in 34.09% of adult and 40.62% of paediatric patients in the post-introduction period.

Table 4.24: Record of timing of culture tests on the antibiotic chart

Timing of culture	**Adult ward (N=88) n (%)**	**Paediatric ward (N=96) n (%)**
Before antibiotic	50 (56.82)	57 (59.38)
After antibiotic	8 (9.09)	0 (0.00)
Not documented	30 (34.09)	39 (40.62)

4.7.3.4 Record of culture and sensitivity results

In the post-introduction period, 3.41% of culture results were appropriately documented on the antibiotic chart in the adult ward, and 25% in the paediatric ward. The remaining 96.59% and 75% of culture results in the adult and paediatric wards respectively remained documented in the patients' records (doctors' notes, discharge summary, daily flow chart or laboratory sheet) and were not transferred onto the antibiotic chart.

4.7.4 Antibiotic utilisation

4.7.4.1 Record of antibiotics

After implementing the antibiotic prescription chart, 73.08% (n=114) of antibiotics were appropriately documented on the antibiotic prescription chart in the adult ward, and 73.73% (n=87) in the paediatric ward (Figure 4.7). Antibiotics were documented simultaneously in both the antibiotic prescription chart and the previously used drug chart in 19.23% (n=12) of adult patients and 11.86% (n=17) of paediatric patients. The antibiotic dose, frequency of administration and route of administration were also documented in the same proportion of patients, as shown in Figure 4.5.

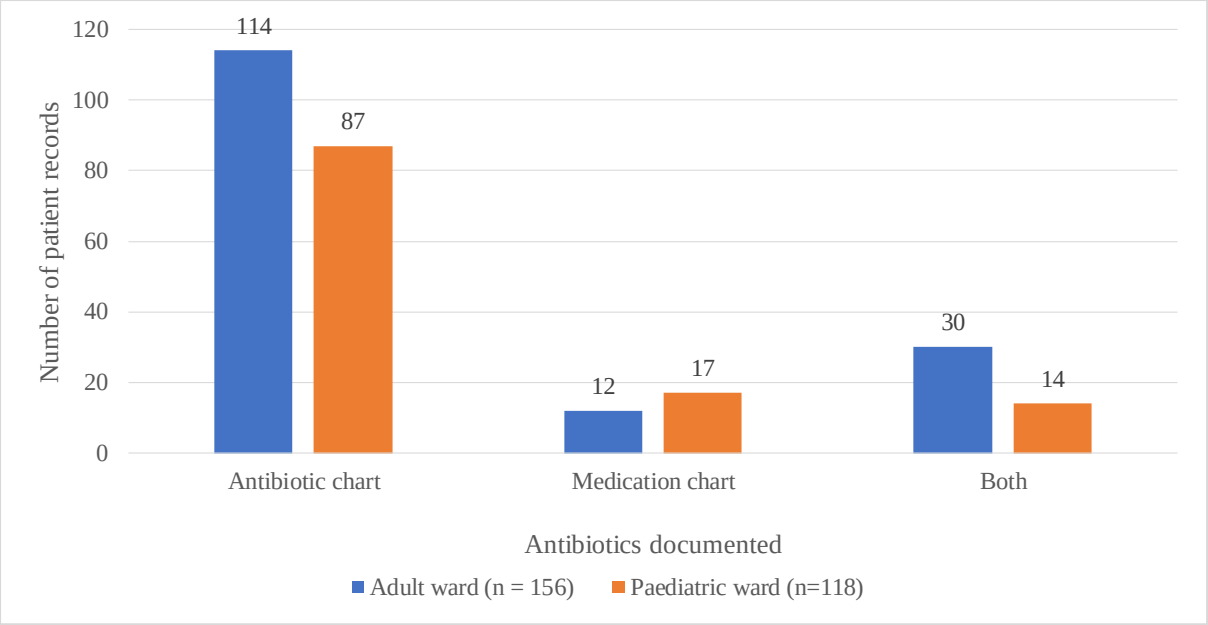

Figure 4.5: Documentation of antibiotics prescribed

4.7.4.2 Record of time of antibiotic prescribing

The time of antibiotic prescribing was indicated in only six antibiotic prescription charts in the adult ward and 20 charts in the paediatric ward (Figure 4.6). The mean hangtime of prescriptions with a documented time of antibiotic prescribing on antibiotic charts in the adult ward was 67.33 minutes and 48.16 minutes in the paediatric ward.

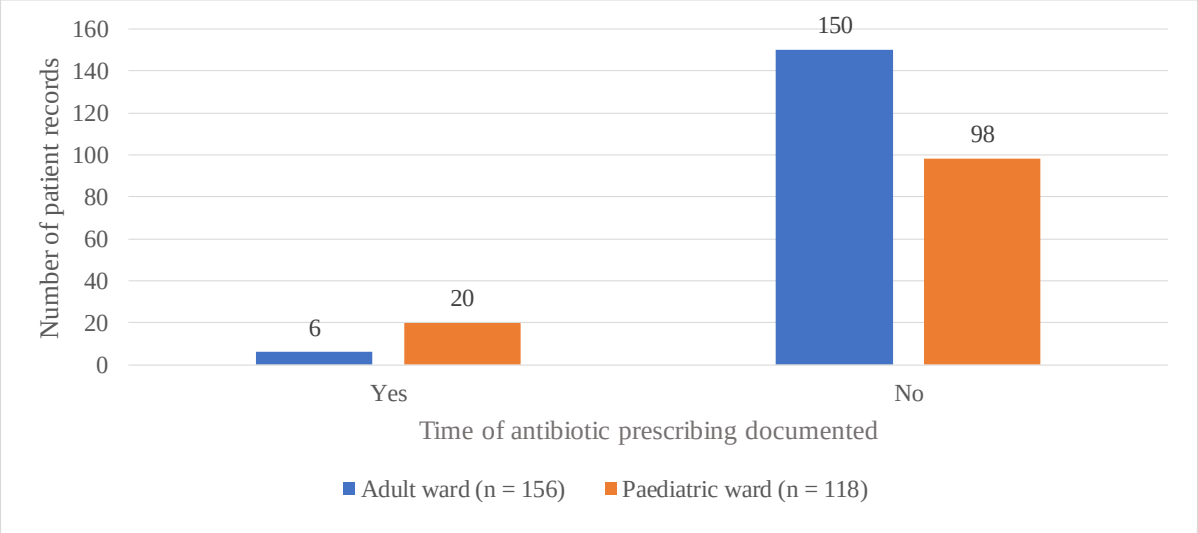

Figure 4.6: Record of time of antibiotic prescribing

4.7.4.3 Record of rationale for antibiotic prescribing

In the post-introduction period, the rationale for prescribing antibiotics was indicated in 31.41% (n = 49) of antibiotic prescription charts in the adult ward, and 50.85% (n = 60) in the paediatric ward (Figure 4.7).

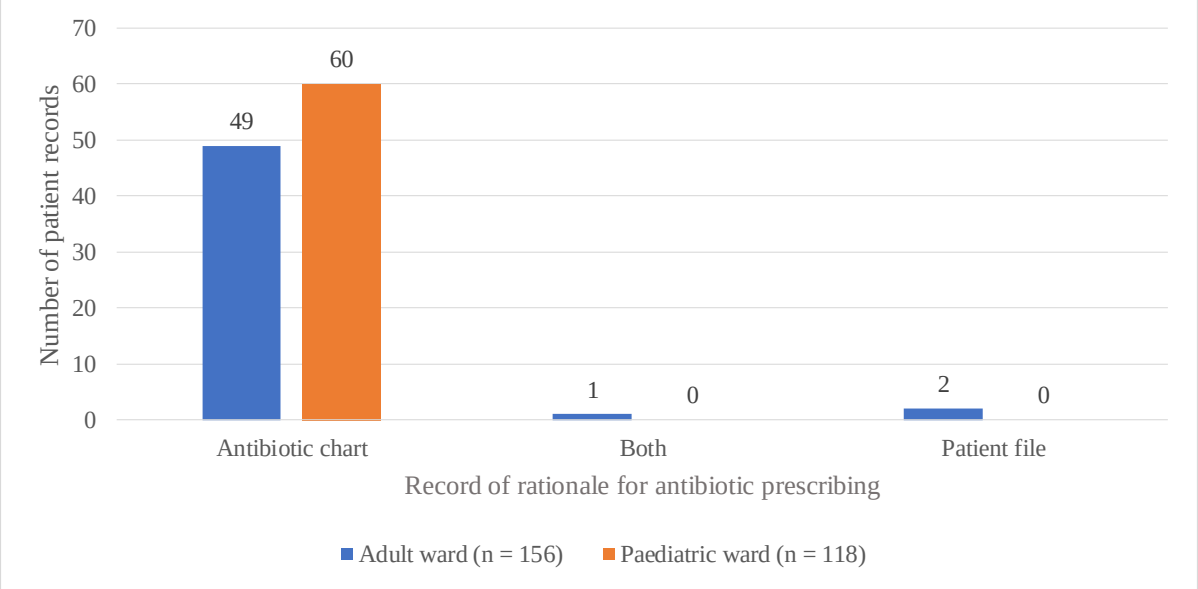

Figure 4.7: Record of rationale for antibiotic prescribing in the post-introduction period

4.8 Concurrent Antibiotic Use

In the pre-introduction period, 33.69% (n=63) and 27.27% (n=51) of patient records indicated the use of two and three concurrent antibiotics respectively while on admission in the adult ward (Table 4.25), while 16.58% (n=38) received more than four antibiotics concurrently. Furthermore, in the post-introduction period, 40.38% (n=63) and 25% (n=39) of patient records documented prescription of two and three concurrent antibiotics, respectively in the adult ward, with 10.90% (n=17) receiving more than four antibiotics simultaneously. In the pre-introduction and post-introduction periods respectively, 90.32% (n=28) and 100% (n=17) of the proportion receiving more than four antibiotics were diagnosed with disseminated or MDR tuberculosis, which requires combination therapy. In the adult ward, two patients were concurrently administered metronidazole intravenously and orally in the pre-introduction period. One was diagnosed with sepsis and the other, gastroenteritis with a duration of eight and two days respectively, with *Clostridium difficile* present in both stool cultures. This combination therapy appears to be a standard procedure at the study site (Johnston *et al.*, 2018).

Table 4.25: Concurrent antibiotic use in the adult ward

Number of concurrent antibiotics	**Pre-introduction n (%)**	**Post-introduction n (%)**
One antibiotic	42 (22.46)	37 (23.72)
Two concurrent antibiotics	63 (33.69)	63 (40.38)
Three concurrent antibiotics	51 (27.27)	39 (25.00)
≥ Four concurrent antibiotics	31 (16.58)	17 (10.90)
Total	**187 (100.00)**	**156 (100.00)**

As mentioned in section 4.4.3, antibiotic use in both study periods was similar in each ward. The most common concurrent antibiotics in the adult ward were amoxicillin/clavulanic acid with azithromycin (Appendix 8). Furthermore, a combination of amoxicillin/clavulanic acid with piperacillin/tazobactam and amoxicillin/clavulanic acid with ceftriaxone was administered once each in the post-introduction period in the adult ward, indicating overlapping coverage for gram-negative organisms.

The paediatric ward recorded 44.07% of patients prescribed only one antibiotic closely followed by those who received two concurrent antibiotics (40.68%) in the pre-introduction period. On the other hand, 50% of patients prescribed antibiotics received two concurrent antibiotics in the post-introduction period (Table 4.26). Three patients were documented to have received four or more concurrent antibiotics each in the paediatric ward in the pre-introduction and post-introduction study periods (Table 4.26) two of which were on anti-tuberculosis medication in each study period. The most administered concurrent antibiotics in the paediatric ward include amikacin plus piperacillin/tazobactam and ampicillin plus gentamycin. This was similar in both study periods. The combination of ampicillin plus gentamycin is effective as a first-line treatment in the management of sepsis in paediatrics and lowering mortality rates (Bibi *et al.*, 2012).

Table 4.26: Concurrent antibiotic use in the paediatric ward

Number of concurrent antibiotics	**Pre-introduction n (%)**	**Post-introduction n (%)**
One antibiotic	52 (44.07)	47 (39.83)
Two concurrent antibiotics	48 (40.68)	59 (50.00)
Three concurrent antibiotics	15 (12.71)	9 (7.63)
≥ Four concurrent antibiotics	3 (2.54)	3 (2.54)
Total	**118 (100.00)**	**118 (100.00)**

4.9 Determinants of antibiotic prescribing

Logistic regression of outcomes that may be associated with antibiotic prescribing is presented in Tables 4.27 and 4.28. From the results, patient records with two or more diagnoses were more likely to be prescribed an antibiotic in the adult ward compared to those with one diagnosis (OR = 2.03, 95% CI: 0.82, 5.73).

Results from the paediatric ward show that patients within the age range of one month and ≤ one year (OR = 3.01, 95% CI: 1.52, 6.00), and those with two or more diagnoses (OR = 3.01, 95% CI: 1.77, 5.22), were at greater odds of receiving an antibiotic.

The multivariate analysis showed a significant association between the number of diagnoses, study period, and being an infant between 29 to 364 days with antibiotic prescribing. The age categorisation in the paediatric ward was adapted from Koopmans *et al*. (2018).

Table 4.27: Determinants of antibiotic use in the adult ward

	Crosstab			Univariate					Multivariate		
Variable	**0, N = 23**	**1, N = 343**	**p-value[1]**	**N**	**Event N**	**OR[2]**	**95% CI[2]**	**p-value**	**OR[2]**	**95% CI[2]**	**p-value**
Sex	12 (52%)	181 (53%)	>0.9	366	343	1.02	0.43, 2.40	0.96	1.29	0.53, 3.13	0.6
Age			0.051	366	343	0.97	0.94, 1.00	**0.027**			
Mean (SD)	45.43 (15.76)	38.86 (12.62)									
Range	26.00, 85.00	18.00, 84.00									
No. of Diagnosis			0.2	366	343			0.13			
1	17 (74%)	200 (58%)				—	—		—	—	
2+	6 (26%)	143 (42%)				2.03	0.82, 5.73		1.96	0.78, 5.61	0.2
Study period			>0.9	366	343			0.85			
Pre-introduction	10 (43%)	156 (45%)				—	—		—	—	
Post-introduction	13 (57%)	187 (55%)				0.92	0.38, 2.15		0.85	0.34, 2.03	0.7

[1]Statistical tests performed: chi-square test of independence; Wilcoxon rank-sum test

[2]OR = Odds Ratio, CI = Confidence Interval

Table 4.28: Determinants of antibiotic use in the paediatric ward

	Crosstab			Univariate					Multivariate		
Variable	**0, N = 100[1]**	**1, N = 236[1]**	**p-value[2]**	**N**	**Event N**	**OR[3]**	**95% CI[3]**	**p-value**	**OR[3]**	**95% CI[3]**	**p-value**
Sex	54 (54%)	155 (66%)	0.037	338	236	1.70	1.06, 2.73	**0.028**	1.63	0.97, 2.73	0.064
Age			<0.001	338	236			**<0.001**			
Neonate (<28 days)	27 (27%)	39 (17%)				—	—		—	—	
Infant (29–364 days)	24 (24%)	120 (51%)				3.46	1.80, 6.73		3.01	1.52, 6.00	0.002
Paediatrics (≥1 year)	49 (49%)	77 (33%)				1.09	0.59, 1.99		0.91	0.48, 1.72	0.8
No. of Diagnosis			<0.001	338	236			**<0.001**			
1	74 (73%)	111 (47%)				—	—		—	—	
2+	28 (27%)	125 (53%)				2.98	1.81, 4.99		3.01	1.77, 5.22	<0.001
Study period			0.018	338	236			**0.012**			
Pre-introduction	66 (65%)	118 (50%)				—	—		—	—	
Post-introduction	36 (35%)	118 (50%)				1.83	1.14, 2.98		2.00	1.19, 3.38	0.009

[1]Statistics presented: n (%)

[2]Statistical tests performed: chi-square test of independence; Fisher's exact test

[3]OR = Odds Ratio, CI = Confidence Interval

4.10 Chapter Conclusion

In summary, similar antibiotics were used in both study periods in each ward as well as the routes of administration. Empiric therapy was mostly employed followed by definitive therapy. There was a decrease in the mean number of antibiotics and duration of antibiotic therapy per patient in the post-introduction period.

The introduction of the antibiotic chart allowed for documentation of parameters in the post-introduction period including the rationale for antibiotic prescribing, renal function tests, infection source and time of antibiotic prescribing, although the rate of documentation varied between both wards. Patient diagnosis, antibiotics, dosage, frequency of administration and route of administration were appropriately recorded on the antibiotic prescription chart in both wards.

The next chapter explains the findings from this study and relates their relevance to existing literature.

CHAPTER 5

5. DISCUSSION

5.1 Introduction

The utilisation of antibiotics after introducing a paper-based antibiotic prescription chart in an academic tertiary hospital in Johannesburg was investigated in this research. This chapter discusses the study findings based on antibiotic use, culture and sensitivity testing, as well as an audit of the antibiotic prescription chart in the selected study wards.

Antibiotic resistance is a direct outcome of antibiotic utilisation as increasing antibiotic exposure to bacteria promotes the selection of resistant pathogens, thereby increasing the chances of antibiotic-resistant bacteria (Gelband *et al.*, 2015). Optimal antibiotic use to reduce the emergence of ABR is advocated for through AMS strategies (Okeke *et al.*, 2005; Sipahi, 2008). The burden of infectious diseases is a worldwide challenge. It is, however, more pronounced in developing countries where resources are limited, coupled with high infection rates (Okeke *et al.*, 2005; USAID, 2012). Research on the use of a dedicated antibiotic prescription chart as an AMS tool to review antibiotic usage is limited to studies conducted by Durbin *et al.* (1981) and Boyles *et al.* (2013). Several studies have evaluated antibiotic use, in conjunction with other AMS strategies (Boyles *et al.*, 2013), however, the actual impact of the antibiotic prescription chart is lacking.

In this study, patient records and antibiotic prescription charts were retrospectively assessed in two wards of the study site. A similar study that reviewed the introduction of AMS ward rounds and a dedicated antibiotic chart in an academic teaching hospital in South Africa reported a 19.6% reduction in antibiotic use, however, it was uncertain about the individual contribution by each strategy (Boyles *et al.*, 2013). The introduction of an antibiotic prescription chart as an AMS strategy is crucial in reducing inappropriate antibiotic use in healthcare institutions. The antibiotic prescription chart serves as a means of surveillance and enables the proper selection of antibiotics when used optimally.

5.2 Demographics

The results of this study reflected a higher proportion of males than females in both wards and study periods. Recent studies of antibiotic utilisation in the hospital setting have similarly shown a greater proportion of males, including 55% of male patients in a medical ward of a

district hospital in Ethiopia (Gube *et al.*, 2017), 54.76% of males in a prospective-observational study in Hyderabad (Ram *et al.*, 2016) as well as 52.4% and 57.3% of males in the pre-intervention and post-intervention period in an assessment of an AMS intervention on antibiotic consumption in Germany (Kreitmeyr *et al.*, 2017). In this study, there was no significant difference between gender in both study periods across the study wards (adult ward p=0.561; paediatric ward p=0.132).

The mean age recorded in this study was significantly greater in the post-introduction period (41.08 ± 14.25 years) as compared to the pre-introduction period (37.77 ± 11.51 years) in the adult ward (p=0.0195). Meanwhile, the mean age of patients in the paediatric ward was greater in the pre-introduction period (1.13 ± 2.35 years) as compared to the post-introduction period (0.89 ± 1.41 years) with no statistically significant difference (p=0.2434). Studies have reported mean ages ranging from 34.2 ± 9.55 years (Demoz *et al.*, 2020) to 65.9 ± 16.6. (Al Shimemeri *et al.*, 2011), as well as 40.4% of patients admitted on a paediatric ward aged less than one year (Versporten *et al.*, 2013).

The average length of hospital stay in the adult ward was 8.52 ± 7.14 and 10.45 ± 9.67 days in the pre-introduction and post-introduction periods respectively (Section 4.2), while that of the paediatric ward was 7.90 ± 7.32 and 8.18 ± 11.48 days in the pre-introduction and post-introduction periods respectively (Section 4.2). There was no significant difference between the length of stay across both study periods in both the adult (p=0.4896) and paediatric wards (p=0.9175). A decreased or constant length of hospital stay after the introduction of an AMS intervention has been reported (Kreitmeyr *et al.*, 2017; Nault *et al.*, 2017). Furthermore, a study that reviewed a pharmacist-led antimicrobial stewardship intervention observed an increase in the length of hospital stay from 19.8 ± 12 in the intervention period to 24.1 ± 13.9 post-intervention with a statistically significant difference (p=<0.001) (Gebretekle *et al.*, 2020). The results of this study revealed a longer length of stay in the post-introduction period across both wards with a statistically significant difference in the adult ward (p=0.0345) but not in the paediatric ward (p=0.8234). This observation in the adult ward is concerning, considering the reduced average number of antibiotics administered in the post-introduction period, as longer stays pose a greater risk of HAI and promote the development of resistant strains (Drew, 2009; Gutema *et al.*, 2018). This finding may be related to a higher proportion of patients receiving other antimicrobials or treatment for comorbid conditions in the post-introduction period when

compared to the pre-introduction period. Also, the increase in the proportion of patients receiving parenteral antibiotics in the paediatric ward may influence the length of stay as several AMS studies have documented a reduced length of stay resulting from the early switch from oral to parenteral antibiotics (Oosterheert *et al.*, 2006; Carratalà *et al.*, 2012).

The most prevalent diagnoses reported in the adult ward in the pre-introduction period were tuberculosis, meningitis, pneumonia and sepsis, while in the post-introduction period, there were mostly cases of pneumonia, tuberculosis, meningitis, and intra-abdominal infections. Meanwhile, cases of pneumonia and sepsis were the most frequent diagnosis in the paediatric ward across both study periods. Pneumonia or lower respiratory tract infections have been named as one of the most common indications for inpatient antibiotic prescribing worldwide (Versporten *et al.*, 2018). Studies suggest that the proportion of individuals requesting medical care due to upper and lower RTIs increases as temperature decreases and may peak during the winter season (Shek and Lee, 2003; Falagas *et al.*, 2008). The data employed in this research was for patients admitted within the winter and spring seasons in South Africa, which may explain the prevalence of respiratory conditions.

5.3 Antibiotic Utilisation

Antibiotics are of great benefit in the treatment of infectious diseases and are commonly prescribed to non-critical hospitalised patients (Fridkin *et al.*, 2014). A total of 93.50% and 93.98% of patient records showed at least one antibiotic received in the pre-introduction and post-introduction periods respectively in the adult ward with no statistically significant difference (p=0.491). Although, studies have reported ranges of antibiotic prescribing of 79% (Amaha *et al.*, 2018), 84% (Hadi *et al.*, 2008) and 82.3% (Atif *et al.*, 2017), the outcome of this study indicates a higher percentage of antibiotic prescribing in the adult ward. This high proportion in the adult ward may be associated with the inclusion of patients receiving anti-tuberculosis treatment, including those on HIV prophylaxis with sulfamethoxazole/trimethoprim, as it is recommended that TB HIV co-infected patients be administered cotrimoxazole prophylaxis regardless of CD4 count (NDoH, 2019). Besides, the adult ward employed in this study was majorly for cases relating to infectious diseases, which may account for the prominent antibiotic use.

In the paediatric ward, on the other hand, antibiotic prescribing decreased by 11.79% in the post-introduction period. The introduction of the antibiotic chart may have contributed to the reduced antibiotic use in the paediatric ward.

5.3.1 Antibiotics prescribed

The most frequently prescribed antibiotics were similar in both study periods of the adult ward and include rifampicin/isoniazid/pyrazinamide/ethambutol, amoxicillin/clavulanic acid, sulfamethoxazole/trimethoprim, and ceftriaxone (Section 4.4.4). An increase in the usage of amoxicillin/clavulanic acid was observed in the adult ward in the post-introduction period (19.96%) compared to the pre-introduction period (16.32%). This finding may be related to the increase in cases of pneumonia in the post-introduction period usually resulting from *Streptococcus pneumoniae* infection (NDoH, 2018b) which sensitivity results showed was sensitive to amoxicillin/clavulanic acid. This trend was also observed in the paediatric ward, although with fewer cases of pneumonia in the post-introduction period. This shows the practice of culture directed antibiotic prescribing which prevents the emergence of ABR. Ceftriaxone (Atif *et al.*, 2017; Krasniqi *et al.*, 2019; Demoz *et al.*, 2020), as well as amoxicillin/clavulanic acid (Johnston *et al.*, 2018; Sarwar *et al.*, 2018), have been reported to be commonly prescribed antibiotics in several studies.

In the adult ward, the use of restricted antibiotics including carbapenems and colistin were reduced in the post-introduction period. These antibiotics require prior authorisation from assigned AMS trained clinicians in various departments of the study site before being dispensed from the pharmacy. This is also an AMS strategy adopted to reduce the unnecessary use of last-resort antibiotics. Restriction of selected antibiotics has led to reduced consumption of antibiotics in the hospital setting (Ng *et al.*, 2008; Tunger *et al.*, 2009).

The most used antibiotics in the paediatric ward were also similar in both study periods, and include ampicillin, gentamycin, and cefotaxime (Section 4.4.4). This is similar to reports from studies conducted in paediatric wards in South African hospitals (Mabila *et al.*, 2016; Koopmans *et al.*, 2018) and an Ethiopian referral hospital (Amaha *et al.*, 2018) where ampicillin and gentamycin were reported to be the most frequently prescribed antibiotics. Empiric treatment of septicaemia and severe pneumonia with gentamycin alongside ampicillin is recommended in the South African Standard Treatment Guidelines (STG) for paediatrics

(NDoH, 2017). This may account for the frequent use of ampicillin and gentamycin, as cases of sepsis and pneumonia were predominant in the paediatric ward over both study periods. The use of amikacin and piperacillin/tazobactam was almost doubled in the paediatric ward in the post-introduction period compared to the pre-introduction period, so also was the frequency of isolation of *Klebsiella pneumoniae*. Although the culture and sensitivity testing only reported sensitivity to amikacin, studies have shown the sensitivity of *Klebsiella pneumoniae* to amikacin and piperacillin/tazobactam (Varghese *et al*., 2016; Saha, 2019).

In reviewing specific cases, patient X was administered three carbapenems within the duration of admission in the adult ward, with one day of imipenem and meropenem administered simultaneously (Table 4.5) in the pre-introduction period. Both imipenem and meropenem are equipotent, as they both share pharmacokinetic similarities. It is recommended that the use of imipenem and meropenem which are classified under the "Watch" group by the WHO in the 2019 Access, Watch and Reserve (AWaRe) classification of antibiotics should be reduced as these have greater resistance potential (NDoH, 2018a; WHO, 2019). Inappropriate exposure to these critically important antibiotics is detrimental to the fight against antimicrobial resistance.

The results arising from this study showed that the mean number of antibiotics per patient in the adult ward was 2.92 ± 2.30 in the pre-introduction period and 2.54 ± 1.62 in the post-introduction period, with no statistically significant difference (p=0.3). On the other hand, an average of 1.60 ± 1.52 antibiotics prescribed in the pre-antibiotic period and 1.31 ± 1.41 in the post-introduction period was documented in the paediatric ward with no statistically significant difference (p=0.054). A varying average number of prescribed antibiotics per in-patient admission has been reported, including, 1.29 (Amaha *et al.*, 2018), 1.4 (Atif *et al.*, 2017), 1.4 (Sarwar *et al.*, 2018) 2.01 (Demoz *et al.*, 2020) and 2.1 (Gutema *et al.*, 2018). A related study that reviewed pharmacist-led AMS intervention reported a statistically significant difference in the mean number of antibiotics per patient in the intervention period 1.78 ± 0.7 and post-intervention 2.83 ± 1.2 (p=0.001) (Gebretekle *et al.*, 2020). A slight decline in the mean number of antibiotics was observed in both wards of this study, which could infer that a longer review period could show a more pronounced effect of the antibiotic prescription chart on antibiotic prescribing. Regular review of antibiotic therapy using the antibiotic prescription chart by a clinical pharmacist and infectious disease physician may ensure optimal antibiotic use.

5.3.2 Duration of antibiotic therapy

The study findings reveal that 60.96% and 55.13% of patients in the adult ward received antibiotics for 1-7 days in the pre-introduction and post-introduction periods respectively. Overall, the duration of antibiotic therapy increased by 1.4 days in the post-introduction period in the adult ward. However, upon further investigation and exclusion of patients on antituberculosis treatment, it was observed that the duration of therapy decreased by 0.42 days in the post-introduction period (from 6.47 ± 5.50 days in the pre-introduction period to 6.05 ± 4.77 days in the post-introduction period). A 2.26% increase in patients receiving rifampicin/isoniazid/pyrazinamide/ethambutol fixed-dose drug combination was observed in the post-introduction period compared to the pre-introduction period. This infers that the increase in patients receiving antituberculosis therapy which is recommended for a duration of six months (and up to nine months in TB meningitis) according to the South African STG on hospital-level (NDoH, 2019) skewed the overall duration of antibiotic therapy. This finding is similar to reports from a study by Amaha *et al.* (2018) which recorded an average duration of 6.36 ± 6.06 antibiotic days but higher than 4.2 ± 2.3 days recorded in another study by Demoz *et al.* (2020). The mean age of patients in the latter study is lower than that of this study. The higher mean age with probable comorbidities may have resulted in this difference in antibiotic duration. Gebretekle *et al.* (2020) reported a significant increase in the average duration of antibiotic therapy from 8.7 ± 6.9 days during the intervention, to 12.8 ± 11.7 days in the post-intervention phase (p=0.002) while a significant difference in the duration of antibiotic therapy was observed from 4.8 ± 3.3 days for patients of physicians who accepted ASP suggestions to 7.9 ± 5.7 days for those who did not accept ASP interventions in another study (p<0.001) (Liew *et al.*, 2012).

On the other hand, 78.81% and 79.66% of patients received antibiotics in the paediatric ward with an average of 6.32 ± 5.45 and 6.82 ± 10.96 antibiotic days in the pre-introduction and post-introduction periods, respectively. Furthermore, the duration of antibiotic therapy decreased by 0.13 days upon exclusion of patients on antituberculosis treatment in the paediatric ward. The duration of antibiotic therapy is often guided by clinical response and prolonged in bloodstream infections (Havey *et al.*, 2013).

5.3.3 Route of administration

The right route of administration for any medication should deliver the quantity necessary to produce the desired result without an adverse outcome (Kuper, 2008). Overuse of parenteral medicines constitutes irrational use of medicines (World Health Organization, 2002). This, alongside the challenges of drug administration, discomfort to patients, increased cost and risk of infection and longer hospital stays makes the oral route a preferred choice (Kuper, 2008). A combination of both oral and parenteral antibiotics was mostly administered to patients in the adult ward in both study periods. The paediatric ward employed mostly parenteral antibiotics in both study periods. The hospital formulary guides antibiotic prescribing. The frequent use of parenteral antibiotics in the paediatric ward may be associated with limited antibiotic choices in the hospital formulary, unavailability of an alternate dosage form of the appropriate antibiotic as well as inadequate antibiotic stock on hand. Despite the possible adverse occurrences associated with the parenteral route of administration, such as the risk of infection and air embolism, parenteral antibiotics have been documented to be the major route of antibiotic administration in several studies (Hadi *et al.*, 2008; Ram *et al.*, 2016; Oduyebo *et al.*, 2017; Amaha *et al.*, 2018; Demoz *et al.*, 2020).

5.3.4 Rationale for antibiotic prescribing

Empiric antibiotic therapy is usually initiated before the outcome of sensitivity testing is obtained and may be reviewed on obtaining the microbiological findings as prompt treatment may improve patient outcomes (Ram *et al.*, 2016). The results of this study indicated that in the adult ward, empirical antibiotic therapy was documented two-fold in the post-introduction period compared to the pre-introduction period. No designated field was provided for documenting this information in the pre-introduction period which may account for this difference. Empiric antibiotics have been widely reported to be the most initiated therapy including a PISA study which recorded empiric antibiotics in 73.5% of patients (Paruk *et al.*, 2012), 86% and 96% in adults and paediatrics respectively in six regional hospitals in Kosovo (Krasniqi *et al.*. 2019) and a cross-sectional study in Ethiopia which reported that 81.5% of the antibiotics prescribed were empiric, while prophylactic use accounted for 2.5% (Gube *et al.*, 2017). Although, 89.84% of antibiotics prescribed did not include a rationale in the pre-introduction period and 66.67% in the post-introduction period, the low percentages of culture targeted therapy in both study wards is concerning as this was less than one-tenth of the study population as illustrated in Tables 4.14 and 4.15. The rationale behind the undocumented

proportion could not be ascertained even when a dedicated field to record this information was provided on the antibiotic chart in the post-introduction period. This could indicate poor adherence to completing the antibiotic prescription chart.

5.4 Culture and Sensitivity Testing

The need for appropriate culture and sensitivity testing in antibiotic selection cannot be overemphasised. It is essential that samples are appropriately and promptly obtained for testing and requested before initiating antibiotic therapy to optimize an accurate diagnosis (Leekha *et al.*, 2011). The proportion of culture and sensitivity tests requested in the post-introduction period increased by 5.07% and 6.78% in the adult and paediatric wards respectively. The introduction of the antibiotic prescription chart may have prompted this improvement in the study wards. This finding is higher than that observed in a paediatric ward of a public hospital in South Africa where laboratory tests were not requested in 69.7% of cases (Mabila *et al.*, 2016).

The most frequently isolated pathogens in the adult ward include *H. influenzae* in the pre-introduction period and Coagulase-negative *Staphylococcus* in the post-introduction period. This observation is similar to reports from several studies which observed *H. influenzae* and coagulase-negative *Staphylococcus* included in the most common organisms isolated in general, medical and ICU wards (Zhanel *et al.*, 2008, 2010). Furthermore, Coagulase-negative *Staphylococcus* and *K. pneumoniae* were frequent in the pre-introduction and post-introduction periods respectively in the paediatric ward. Studies have reported a high prevalence of *K. pneumoniae* isolated in the hospital setting (Radji *et al.*, 2011; Agaba *et al.*, 2017). Cases of colistin-resistant *A. baumannii* were recorded in this study (once in the pre-introduction period in the adult ward and once each in both study periods in the paediatric ward) which is concerning as colistin is considered a last resort antibiotic. The discovery of mobile colistin resistance (*mcr*) genes have been reported in *A. baumannii* and represent an emerging challenge that requires proper monitoring (Martins-Sorenson *et al.*, 2020; Wang *et al.*, 2020). *Acinetobacter baumannii* has also been commonly associated with hospital-acquired infections as well as MDR strains (Brink *et al.*, 2006).

5.5 Infection Markers

The use of infection markers in aiding the clinical decision to initiate or discontinue antibiotics has increased over time (Hayashi and Paterson, 2011; Foushee *et al.*, 2012). CRP is commonly employed in diagnosing bacterial infections (Huang *et al.*, 2013) and PCT results have been shown to guide antibiotic use in patients with lower respiratory tract infections (Christ-Crain *et al.*, 2004), ICU patients (Hochreiter *et al.*, 2009) and community-acquired pneumonia (Christ-Crain *et al.*, 2006). In this study, documentation of CRP testing was similar in the adult ward across both study periods, while 25.13% and 16.67% of patient records had a PCT test done. A statistically significant reduction in the proportion of PCT tests in the post-introduction period was observed (p=0.039). This decrease could result from the cost implication of conducting the test which costs over R300 (Mendelson, 2015; Supply Chain Management Bid Adjudication Committee, 2018), as well as the antibiotic prescription chart not containing a field for documenting infection markers.

In the paediatric ward, 86.44% and 92.37% of patient records documented daily CRP tests, while 8.47% and 6.78% had a PCT test done in the pre-introduction and post-introduction periods respectively. Only a few studies have employed the use of biomarkers due to costs and insufficient awareness in some parts of the developing world (Oduyebo *et al.*, 2017).

In addition to the above study findings, the use of the antibiotic prescription chart in the post-introduction period was also reviewed. Dedicated antibiotic prescription charts are useful in improving antibiotic prescribing. It encourages clinicians to record the indication (prophylactic, empiric, definitive), dosage, duration and frequency of administration, allergy and abnormal renal or hepatic function (Marr *et al.*, 1988). Successful implementation of an antibiotic prescription chart may impact positively on compliance to appropriate prescribing and usage of antibiotics. The antibiotic chart is designed to include information relating to patient demographics (name, age, weight, ward, gender and renal function), diagnosis, infection source, antibiotics (antibiotic, dosage, route of administration, dosing frequency, time of prescribing and duration of therapy), the rationale for antibiotic prescribing as well as culture and sensitivity testing (timing of culture testing, isolated pathogen, susceptible and resistant antibiotics). Compliance with the documentation of clinical indicators on the antibiotic prescription chart is necessary to improve the review of antibiotic therapy using this AMS strategy (NDoH, 2018a).

The outcome of this study shows that the commonly omitted fields on the antibiotic prescription chart in the adult ward include a record of culture and sensitivity results (96.59%), time of antibiotic prescribing (96.15%), age (95.51%), weight (92.31), allergies (91.03%), record of renal function (GFR/CrCl) (69.23%) rationale for antibiotic prescribing (68.59%), record of infection source (48.72%) and timing of culture tests (34.09%). This suggests that the documentation of relevant information on the antibiotic prescription chart was inadequate. There is, however, the potential for improvement on appropriate documentation of information on the antibiotic prescription chart as several fields were left incomplete on the antibiotic prescription chart. Prescribers need to be sensitised on the need to complete all fields contained in the antibiotic prescription chart as this will assist in appropriate antibiotic selection and use. The commitment of clinical staff also plays an important role in achieving consistent and optimum benefit from the use of the antibiotic prescription chart.

In the paediatric ward, the most omitted fields include age (100%), record of renal function (GFR/CrCl) (97.46%), time of antibiotic prescribing (83.05%), record of culture and sensitivity results (75%), the rationale for antibiotic prescribing (49.15%), record of infection source (47.46%), and timing of culture tests (40.62%). A similar study that audited the antibiotic prescription chart reported commonly omitted fields to include weight (45%), estimated glomerular filtration rate (36%) and allergies (32%) (Boyles *et al.*, 2013). Antibiotics are frequently administered per kilogram body weight in paediatric patients, and this could account for the increased rate of documentation of weight values on the antibiotic prescription chart in the paediatric ward when compared to the adult ward.

A probable reason for this incomplete documentation could be the inconvenient and time-consuming process of completing the chart as they may have several patients to attend to within a limited time frame. A computerized data entry system may improve the use and convenience of the antibiotic prescription chart (Drew, 2009).

Documentation of antibiotics, as well as the dosage, route of administration and duration of therapy, were simultaneously recorded on both the antibiotic prescription chart and the previously used drug chart in 19.23% of adult patients and 11.86% of paediatric patients in the post-introduction period. This could be due to antibiotics being initiated in a previous ward that

does not employ the antibiotic prescription chart and continued in the study wards, or unavailability of the antibiotic prescription chart at the time of admission and subsequent transfer unto the antibiotic prescription chart upon availability. A uniform medium for documentation is necessary across all departments in the hospital to reduce the likelihood of errors and duplicate information.

5.6 Chapter Summary

The outcome of this study indicates that the introduction of the antibiotic prescription chart led to a decrease in the mean number of antibiotics administered per patient and duration of antibiotic therapy in both study wards, as well as a statistically significant reduction in the proportion of patients receiving antibiotics in the paediatric ward.

Evidence for proper implementation of the antibiotic prescription chart in this study is lacking. The antibiotic prescription chart is currently not being used to its full potential with poor documentation practices evident. The inclusion of an educational program emphasizing the benefit of the antibiotic prescription chart as well as timely reviews by the AMS team may have a substantial impact on antibiotic utilisation.

CHAPTER 6

6. CONCLUSION

6.1 Introduction

This chapter highlights the limitations of the study, as well as recommendations for practice at the study site and future research. The key findings and study conclusions are also included in this chapter.

AMR is inevitable by nature. However, rational use of antibiotics is achievable by implementing proper AMS strategies alongside regular surveillance. This study has revealed that an antibiotic prescription chart can positively impact antibiotic prescribing and improve documentation practices within a hospital setting.

6.2 Study Limitations

The data collection process for this study was done manually by the researcher. Each patient record had to be thoroughly assessed to extract the required data, handwritten on the data collection tool (Appendix 1) and subsequently captured on a Microsoft Excel spreadsheet, validated and analysed. This is unlike the South African private health sector where electronic health records are available for easy data extraction. CMJAH stores scanned PDF files of patient records in a dedicated document management system on computers in the records department. This was a tedious and stressful exercise that significantly prolonged the data collection stage of the study, especially during the COVID-19 pandemic lockdown.

In the pre-implementation study period, some of the variables required were missing as there was no consistency in documenting patient information. Information was captured in various documents of the patient's records. It was also difficult to trace missing data and files, as the hard copies of the files are scanned and kept in the record department for a period of three months after patients' discharge or demise and thereafter, they are archived. Prescribers and nurses could also not be consulted to clarify entries and cases of seemingly unclear prescriptions, as the prescriber could have a valid reason for prescribing such medicine to specific patients. This was due to the retrospective nature of the research.

In the wards observed in this study, adherence to the antibiotic chart was insufficient, and as such, this study may not have entirely reflected the true picture of the health sector based on

the data collected. Variables described in Section 5.5 were not routinely indicated. Prescribers may have made mistakes or omissions that were corrected before administration of the antibiotics which the researcher is not aware of. Also, the researcher was unable to confirm data with the prescriber due to the retrospective nature of the study. As such, the findings of this study cannot be generalised because it was conducted in two wards in a single public hospital setting over a short review period. These findings do not necessarily reflect the use of the antibiotic chart in other settings or throughout the study site.

Another limitation of this study was the fact that patients' comorbid conditions, chronic and immunosuppressed conditions were not linked to antibiotic prescribing, including prophylaxis with sulfamethoxazole/trimethoprim in patients with HIV which may have influenced some of the research findings such as the duration of antibiotic therapy and number of antibiotics prescribed. It would be beneficial for physicians to indicate the rationale for which antibiotics are prescribed as this will improve accountability of antibiotic prescribing.

6.3 Recommendation

Frequent training and education of clinicians and nursing staff on the need for optimal antibiotic prescribing and administration, timeous audit and monitoring to ensure adherence to the use of the antibiotic prescription chart is encouraged. It is recommended that a computerised antibiotic chart system with automated features such as time of prescription, a linking laboratory results system, and mandatory fields should be put in place which may improve compliance and timeliness. An electronic record system would also ease the data collection process and also allow for a remote exercise for future researchers. Active involvement of the AMS team including a clinical pharmacist with infectious diseases training should be incorporated into the use of the antibiotic prescription chart to improve antibiotic use.

It is recommended that further studies be carried out on the challenges and perception of clinicians regarding the use of the antibiotic prescription chart as well as the effect of introducing an antibiotic prescription chart on antibiotic prescribing habits in ensuring rational antibiotic use. There is also a need to assess the appropriateness of antibiotic use impacted by the introduction of the antibiotic prescription chart as well as the prescribing pattern of antibiotics following the implementation of the antibiotic prescription chart using WHO

prescribing indicators. Besides, considering the relatively short study periods, the long-term effects of introducing an AMS strategy need to be further investigated. After further continuous and deliberate training and education, antibiotic utilisation should be reviewed over time, as there is the possibility of better outcomes in a multi-strategic AMS setting. The impact of the antibiotic prescription chart on antibiotic resistance, and the appropriateness of concurrent antibiotic use with regards to diagnosis was also not explored, and this may be another subject for future research.

6.4 Conclusion

The global challenge of antibiotic resistance is far from being solved as new resistance patterns are emerging. Practices such as AMS strategies have impacted in controlling and managing this problem. This study has reviewed antibiotic use in a public sector hospital following the introduction of an antibiotic prescription chart which is important in assessing the level of understanding and implementation of this AMS tool and provides guidance for the progression of AMS practices. In this study, diagnosis and antibiotics prescribed remained similar in each ward across both study periods. Furthermore, the findings of this study show an improvement in the average number of antibiotics prescribed, duration of antibiotic therapy, the frequency of culture and sensitivity tests requested and documentation of relevant parameters after the antibiotic chart was introduced. The use of an antibiotic chart in a public sector healthcare facility is feasible. There is significant potential for correctly implementing the antibiotic prescription chart, alongside regular training and monitoring by the AMS team which could further improve antibiotic use.

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Appendix 1: Data collection tool

Modified version of the Charlotte Maxeke Johannesburg Academic Hospital Antimicrobial Prescription Chart

Study number:	Age:	Renal function (eGFR/CrCl)	
	Weight:	Allergies and adverse drug reactions	
Hospital number:	Sex:	Ward: Adult Paediatric	Data source: Patient file Paper chart

Primary diagnosis:								
Infection Episode no.	Pneumonia		UTI		Meningitis		Line infection	
	Cellulitis		Intra-abdominal Infection		Bacteraemia		Other (please specify)	
Source: *(Tick)*	Community acquired (<48 hrs of admission)		Hospital acquired (>48 hrs of admission)		Not specified			
Cultures:*(Tick)*	Sent before antibiotic		Sent after antibiotic		Not sent			
SEND APPROPRIATE CULTURES BEFORE PRESCRIBING ANTIBIOTICS								

REVIEW ON DAYS 3, 5 AND 7					Initial of Nurse Administering Antibiotic							
Empiric *(Tick)* *(3 DAYS)*	**Approved medicine name/Generic Equivalent**	Dose	Route	Frequency	Day	1	2	3	4	5	6	7
					Date			Review		Review		Review
					Time							
Definitive *(Tick)*	Start date: Time:		Stop date:		Time							
Empiric *(Tick)* *(3 DAYS)*	**Approved medicine name/Generic Equivalent**	Dose	Route	Frequency	Day	1	2	3	4	5	6	7
					Date			Review		Review		Review
					Time							
Definitive *(Tick)*	Start date: Time:		Stop date:		Time							
Empiric *(Tick)* *(3 DAYS)*	**Approved medicine name/Generic Equivalent**	Dose	Route	Frequency	Day	1	2	3	4	5	6	7
					Date			Review		Review		Review
					Time							
Definitive *(Tick)*	Start date: Time:		Stop date:		Time							

Once only/Loading dose

Indication		Medicine	Dose	Route	Date & time	Pharmacy	Time given
Prophylactic ***(Tick)***							
Empiric ***(Tick)***							
Definitive ***(Tick)***							
Prophylactic ***(Tick)***							
Empiric ***(Tick)***							
Definitive ***(Tick)***							
Prophylactic ***(Tick)***							
Empiric ***(Tick)***							
Definitive ***(Tick)***							

Microscopy and culture results

Date	**Site***	**Pathogen/Specimen's lab Code**	**Sensitivities**

*BC = blood culture; *MSU = midstream urine; *CSU = catheter specimen urine; *CSF = cerebrospinal fluid; *PS = pus swab; *BM = bone marrow; *JA = joint aspirate; *TA = tracheal aspirate; *SP = sputum; Tissue Biopsy Culture (Biopsy), Fluid (list type)

Specify if another site:

Appendix 2: Wits HREC clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Ms Habibat Salau

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190711

NAME: (Principal Investigator)	Ms Habibat Salau
DEPARTMENT:	Pharmacy and Pharmacology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A review of antibiotic utilisation following the introduction of an electronic antibiotic prescription chart in the infectious diseases ward of an academic tertiary hospital in Johannesburg
DATE CONSIDERED:	26/07/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	D Johnston, R Khan, A Orchard and S Stacey
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/10/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms H Salau

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190711

NAME: (Principal Investigator)	Ms H Salau
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Medical School University
PROJECT TITLE:	A review of antibiotic utilisation following the introduction of an antibiotic prescription chart in an academic tertiary hospital in Johannesburg Study title change noted on 2020/06/24
DATE CONSIDERED:	2019/07/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs D Johnson, R Khan, A Orchard & S Stacey
APPROVED BY:	CB Penny Dr CB Penny, Chairperson: HREC (Medical)
DATE OF APPROVAL:	2019/10/17

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 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 **July** and will therefore reports and re-certification will be due early in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

Appendix 3: CMJAH study approval letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011): 488-4812
Email: Nolwazi.Mzila@gauteng.gov.za
13th November 2019

GP_201911_021

Dear Habibat Salau

STUDY TITLE: A Review of Antibiotic Utilisation Following the Introduction of an Electronic Antibiotic Chart in the Infectious Diseases Ward of an Academic Tertiary Hospital in Johannesburg.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 13/11/2019

Approved/**not approved**

Ms. G. Bogoshi
Chief Executive Officer
Date: 13-11-2019

Appendix 4: Approval letter from the head of paediatrics and child health department

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

FACULTY OF HEALTH SCIENCES

Department of Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

ENQUIRIES : **Prof MC Mulaudzi**
TEL : **011 488 4246/ 4637**
EMAIL : **Mphelekedzeni.Mulaudzi@wits.ac.za**

Date: 10 March 2020

To: Human Research Ethics Committee (HREC)-WITS

Dear Madam/Sir

Permission to conduct research in Paediatrics and Child Health Department at CMJAH

The Department of Paediatrics and Child Health at Charlotte Maxeke Johannesburg Academic hospital give permission the researcher/s to conduct research in the department as stated below:

Research Title: "A review of Antibiotic Utilisation following the introduction of an Electronic Antibiotic Chart in the Infectious Diseases Ward of an Academic Tertiary Hospital in Johannesburg".

Investigator: **Ms. Habibat Salau**

Supervisor/s: **D Johnston, R Khan, A Orchard and S Stacey**

This permission is given in support to your application to the WITS-HREC. The researcher/s cannot start collecting data without the clearance certificate from the HREC.

Mphelekedzeni Caroline Mulaudzi
Adjunct Professor
Head of Department, CMJAH

11/03/2020
Date

Appendix 5: Approval letter from the head of the internal medicine department

Department of Internal Medicine

7 York Road, Parktown, 2193, South Africa •Telegrams 'Witsmed' •Fax: 488 4672 •Tel: 488 3840 •

Division of Infectious Diseases
Department of Internal Medicine
Charlotte Maxeke Johannesburg Academic Hospital
(011) 488 3497
(011) 488 3556

27 August 2019

Dear Ms Salau et al,

Re. **"A review of antibiotic utilisation following the introduction of an electronic antibiotic prescription chart in the infectious diseases ward of an academic tertiary hospital in Johannesburg."**

I am pleased to grant you permission to conduct your research in ward 497 at Charlotte Maxeke Johannesburg Academic Hospital pending approval from the CEO and the HREC

Please ensure that there is no disruption to delivery of clinical services.

Yours sincerely

Prof Adam Mohamed
MBBCh (WITS), FCP(SA), Cert Gastro (SA)
Principal Physician Consultant, Gastroenterologist
Clinical Head Medical Gastroenterology and Hepatology
Clinical Head Internal Medicine
Charlotte Maxeke Johannesburg Academic Hospital
Cell: 083 469 2802 (#6585) Tel: 011-488 3554
E-mail: adam.mahomed@wits.ac.za

Appendix 6: Research protocol approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

20 February 2020
Person No: 1686840
TAA

Miss HD Salau
78A Lewis Street
Lagos
Nigeria

Dear Miss Habibat Salau

Master of Pharmacy: Change of title of research

I am pleased to inform you that the following change in the title of your Dissertation for the degree of **Master of Pharmacy** has been approved:

From:	**A review of antibiotic utilisation following the introduction of an electronic antibiotic prescription chart in the infectious diseases ward of an academic tertiary hospital in Johannesburg.**
To:	**A review of antibiotic utilisation following the introduction of an antibiotic prescription chart in an academic tertiary hospital in Johannesburg.**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 7: List of diagnoses

	Diagnosis	**Frequency in this study**
1.	Acute bronchospasm	1
2.	Acute gastritis	1
3.	Acute gastroenteritis	22
4.	Acute infection	1
5.	Acute kidney injury	1
6.	Acute seizure	1
7.	Anomalous left coronary artery from the pulmonary artery	1
8.	Anaemia	4
9.	Apnoea	4
10.	Aspiration pneumonia	1
11.	Asthma exacerbation	4
12.	Bacteraemia	11
13.	Bacterial meningitis	16
14.	Biliary atresia	5
15.	Bronchiolitis	13
16.	Bronchitis	1
17.	Bronchopneumonia	42
18.	Bullous impetigo	1
19.	*Clostridium difficile*	3
20.	Cardiac catheterization	1
21.	Cardiac failure	1
22.	Cellulitis	4
23.	Cerebral abscess	1
24.	Chemical pneumonitis	1
25.	Cholecystitis	1
26.	Chronic diarrhoea	1
27.	Chronic gastroenteritis	4
28.	Chronic kidney disease	5

	Diagnosis	Frequency in this study
29.	Chronic liver disease	4
30.	Chronic lung disease	3
31.	Communicating hydrocephalus	1
32.	Complicated meningitis	1
33.	Confusion	1
34.	Congenital hypothyroidism	1
35.	Congenital nephrotic syndrome	1
36.	Conjunctivitis	1
37.	Croup	7
38.	Cryptococcal meningitis	2
39.	Cystic biliary atresia	1
40.	Cystic fibrosis	1
41.	Cystinosis	1
42.	Deep fungal sepsis	1
43.	Diarrhoea	1
44.	Drug-induced liver injury	8
45.	Disseminated crypt meningitis	1
46.	Disseminated cryptococcal infection	1
47.	Disseminated TB	60
48.	Drowning	1
49.	Eczema	1
50.	Empyema	7
51.	Epilepsy	2
52.	Epistaxis	1
53.	Failure to thrive	2
54.	Feeding intolerance	1
55.	Follicular tonsillitis	1
56.	Fungal sepsis	4
57.	Gastro-oesophageal reflux disease	1
58.	Gram-negative sepsis	1

	Diagnosis	**Frequency in this study**
59.	Headache	2
60.	Henoch-Schonlein purpura	1
61.	Hodkins lymphoma	1
62.	Hypertension	2
63.	Hypocalcaemia	1
64.	Hypothyroidism	1
65.	Inflammatory bowel syndrome	1
66.	Intra-abdominal infection	10
67.	Iron deficiency anaemia	1
68.	Jaundice	2
69.	Kaposi sarcoma	1
70.	Left breast mastitis	1
71.	Line infection	2
72.	Liver failure	1
73.	Lobar pneumonia	1
74.	Lower respiratory tract infection	18
75.	Lung abscess	1
76.	Lymphoma	6
77.	Malaria	1
78.	MDR tuberculosis	3
79.	Membranous glomerulonephritis	1
80.	Meningitis	47
81.	Moderate acute malnutrition	1
82.	Moderate respiratory distress	1
83.	Mouth ulcers	1
84.	MRSA sepsis	1
85.	Multicystic dysplastic kidney	1
86.	Multilobar pneumonia	3
87.	Myocarditis	1
88.	Neck mass	1

	Diagnosis	**Frequency in this study**
89.	*Neisseria* septicaemia	1
90.	Neonatal jaundice	12
91.	Neonatal sepsis	25
92.	Nephrotic syndrome	1
93.	Neurofibromatosis	1
94.	Non-accidental injury	1
95.	Nosocomial infection	1
96.	Nosocomial pneumonia	3
97.	Nosocomial sepsis	5
98.	Obstructive uropathy	1
99.	Oral candidiasis	1
100.	Otitis media	3
101.	Pancytopenia	1
102.	Parapneumonic effusion	1
103.	Patent ductus arteriosus	1
104.	Pelvic cellulitis	1
105.	Pericardial effusion	1
106.	Pharyngitis	1
107.	Pleural effusion	12
108.	Pneumococcus	1
109.	Pneumocystis pneumonia	3
110.	Pneumonia	128
111.	Pneumothorax	1
112.	Poison ingestion	1
113.	Polycystic kidney	1
114.	Post kidney transplant	2
115.	Post liver transplant	4
116.	Post TB bronchiectasis	3
117.	Posterior urethral valve	1
118.	Prostate cancer	1

	Diagnosis	**Frequency in this study**
119.	Prune belly syndrome	2
120.	*Pseudomonas* colonisation	1
121.	*Pseudomonas* sepsis	1
122.	Pulmonary atresia	1
123.	Pulmonary TB	103
124.	Pyrexia of unknown origin	1
125.	Recurrent sepsis	1
126.	Recurrent UTI	1
127.	Renal dysfunction	4
128.	Renal failure	1
129.	Resistant TB	1
130.	Rickets	3
131.	Rifampicin resistant TB	4
132.	Right empyema	1
133.	*Salmonella* bacteraemia	1
134.	*Salmonella* sepsis	1
135.	Secondary sepsis	1
136.	Seizures	9
137.	Sepsis	35
138.	Severe acute malnutrition	4
139.	Severe bronchiolitis	2
140.	Severe malnutrition	2
141.	Sexual abuse	1
142.	Shone's anomaly	1
143.	Sickle cell anaemia	2
144.	Skin abscess	1
145.	Spastic diplegia	1
146.	Spontaneous pneumothorax	1
147.	*Staphylococcus aureus* skin infection	2
148.	Status epilepticus	1

	Diagnosis	Frequency in this study
149.	Stevens-Johnson syndrome	2
150.	Stroke	1
151.	Symptomatic anaemia	1
152.	Syphilis	2
153.	Trisomy 21	1
154.	TB abdomen	4
155.	TB bronchiectasis	2
156.	TB drug-induced liver injury	4
157.	TB Immune reconstitution inflammatory syndrome	4
158.	TB meningitis	11
159.	TB pericardial effusion	2
160.	TB pericarditis	4
161.	Temporal cyst	1
162.	Thrombocytosis	1
163.	Toxoplasma IgG positive	1
164.	Tricuspid atresia	1
165.	Type 1 diabetes	1
166.	UGIT bleed	1
167.	Unconjugated hyperbilirubinemia	1
168.	URTI	1
169.	UTI	25
170.	UTI prophylaxis	1
171.	UTI sepsis	1
172.	Varicella pneumonia	1
173.	Varicella zoster	1
174.	Ventricular septal defect	1
175.	Viral meningitis	4
176.	Viral pneumonia	1
177.	Viral URTI	1
178.	Visceral myopathy	1

	Diagnosis	**Frequency in this study**
179.	Ventricular septal defect	2

Appendix 8: Concurrent antibiotics used in this study

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
Adult ward	0	1	Amikacin (IV)	Ceftriaxone (IV)		
	0	1	Amikacin (IV)	Piperacillin/tazobactam (IV)		
	0	5	Amoxicillin/clavulanic acid (IV)	Sulfamethoxazole/trimethoprim (PO)		
	2	3	Sulfamethoxazole/trimethoprim (PO)	Rifampicin/isoniazid (PO)		
	0	3	Amoxicillin/clavulanic acid (IV)	Azithromycin (IV)		
	0	1	Amoxicillin/clavulanic acid (IV)	Amikacin (IV)		
	0	1	Amoxicillin/clavulanic acid (IV)	Rifampicin/isoniazid (PO)		
	0	1	Amoxicillin/clavulanic acid (PO)	Ceftriaxone (IV)		
	6	13	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)		
	0	1	Amoxicillin/clavulanic acid (IV)	Piperacillin/tazobactam (IV)		
	1	1	Amoxicillin/clavulanic acid (IV)	Metronidazole (PO)		
	0	1	Rifampicin (PO)	Moxifloxacin (PO)		
	1	0	Rifampicin/isoniazid (PO)	Ertapenem (IV)		
	0	1	Rifampicin/isoniazid (PO)	Flucloxacillin (PO)		
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ciprofloxacin (PO)		
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Azithromycin (PO)		
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Cefazolin (IV)		
	1	0	Rifampicin/isoniazid pyrazinamide/ethambutol (PO)	Vancomycin (IV)		
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Meropenem (IV)		
	10	7	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (IV)		
	2	3	Rifampicin/isoniazid/	Amoxicillin/clavulanic acid (PO)		

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
			pyrazinamide/ethambutol (PO)			
	14	10	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)		
	2	2	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Piperacillin/tazobactam (IV)		
	1	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Metronidazole (PO)		
	5	11	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)		
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Cloxacillin (IV)		
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Levofloxacin (PO)		
	2	0	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)		
	6	0	Sulfamethoxazole/trimethoprim (PO)	Ceftriaxone (IV)		
	1	0	Sulfamethoxazole/trimethoprim (PO)	Cefotaxime (IV)		
	1	0	Sulfamethoxazole/trimethoprim (PO)	Piperacillin/tazobactam (IV)		
	0	1	Vancomycin (IV)	Ceftriaxone (IV)		
	1	0	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)	Metronidazole (PO)	
	2	6	Amoxicillin/clavulanic acid (IV)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (PO)	
	1	0	Azithromycin (PO)	Piperacillin/tazobactam (IV)	Linezolid (IV)	
	1	0	Doxycycline (PO)	Metronidazole (PO)	Ceftriaxone (IV)	
	2	0	Ethambutol (PO)	Moxifloxacin (PO)	Kanamycin (IM)	
	4	7	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)	
	4	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)	Cefotaxime (IV)	

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
	1	0	Moxifloxacin (PO)	Amikacin (IV)	Ethambutol (PO)	
	1	0	Metronidazole (PO)	Vancomycin (PO)	Moxifloxacin (PO)	
	1	0	Metronidazole (PO)	Sulfamethoxazole/trimethoprim (PO)	Piperacillin/tazobactam (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Piperacillin/tazobactam (IV)	
	2	0	Sulfamethoxazole/trimethoprim (PO)	Rifampicin/isoniazid (PO)	Piperacillin/tazobactam (IV)	
	0	1	Sulfamethoxazole/trimethoprim (PO)	Ethambutol (PO)	Rifampicin (PO)	
	0	1	Rifampicin/isoniazid (PO)	Amikacin (IV)	Amoxicillin/clavulanic acid (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Ethambutol (PO)	Rifampicin/isoniazid (PO)	
	1	0	Rifampicin/isoniazid (PO)	Ethambutol (PO)	Azithromycin (PO)	
	3	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ampicillin (IV)	Ceftriaxone (IV)	
	2	2	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Sulfamethoxazole/trimethoprim (PO)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)	Doxycycline (PO)	
	8	2	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Ceftriaxone (IV)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (IV)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)	Moxifloxacin (PO)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin (PO)	Clarithromycin (PO)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (PO)	
	3	0	Rifampicin/isoniazid/	Sulfamethoxazole/trimethoprim (PO)	Cefotaxime (IV)	

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
			pyrazinamide/ethambutol (PO)			
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ethambutol (PO)	Moxifloxacin (PO)	
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Ceftriaxone (IV)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Metronidazole (PO)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Piperacillin/tazobactam (IV)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)	Metronidazole (PO)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (PO)	Metronidazole (PO)	
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Ceftriaxone (IV)	Piperacillin/tazobactam (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Piperacillin/tazobactam (IV)	Clindamycin (IV)	
	1	2	Sulfamethoxazole/trimethoprim (PO)	Rifampicin/isoniazid (PO)	Amoxicillin/clavulanic acid (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	Ceftriaxone (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	Rifampicin/isoniazid (PO)	
	0	4	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)	Cefazolin (IV)
	1	0	Azithromycin (PO)	Ethambutol (PO)	Ethionamide (PO)	Moxifloxacin (PO)
	1	0	Amoxicillin/clavulanic acid (IV)	Sulfamethoxazole/trimethoprim (PO)	Metronidazole (PO)	Ciprofloxacin (IV)
	0	1	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)	Ethambutol (PO)	Moxifloxacin (PO)
	0	1	Ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Moxifloxacin (PO)	Isoniazid (PO)
	1	0	Ethambutol (PO)	Isoniazid (PO)	Kanamycin (IM)	Moxifloxacin (PO)
	0	1	Ethambutol (PO)	Azithromycin (PO)	Ertapenem (IV)	Moxifloxacin (PO)
	0	1	Ethambutol (PO)	Amikacin (IV)	Isoniazid (PO)	Moxifloxacin (PO)
	0	1	Ethambutol (PO)	Clofazimine (PO)	Levofloxacin (PO)	Pyrazinamide (PO)

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
	1	0	Rifampicin (PO)	Ethambutol (PO)	Moxifloxacin (PO)	Piperacillin/tazobactam (IV)
	1	0	Rifampicin (PO)	Ethambutol (PO)	Isoniazid (PO)	Moxifloxacin (PO)
	1	0	Rifampicin (PO)	Colistin (IV)	Metronidazole (PO)	Vancomycin (PO)
	1	0	Rifampicin/isoniazid (PO)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (PO)	Amoxicillin/clavulanic acid (IV)
	1	0	Rifampicin/isoniazid (PO)	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)	Metronidazole (PO)
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Metronidazole (PO)	Amoxicillin/clavulanic acid (IV)
	2	2	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (PO)	Amoxicillin/clavulanic acid (IV)
	0	1	Isoniazid (PO)	Bedaquiline (PO)	Clofazimine (PO)	Levofloxacin (PO) Pyrazinamide (PO)
	1	0	Ethambutol (PO)	Ethionamide (PO)	Isoniazid (PO)	Kanamycin (IM) Moxifloxacin (PO) Pyrazinamide (PO) Terizidone (PO)
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Ampicillin (IV)	Ceftriaxone (IV) Metronidazole (IV)
	0	1	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Piperacillin/tazobactam (IV)	Amikacin (IV) Vancomycin (IV)
	0	1	Ethambutol (PO)	Ceftriaxone (IV)	Ethionamide (PO)	Moxifloxacin (PO) Metronidazole (PO)
	1	0	Rifampicin/isoniazid/ pyrazinamide/ethambutol (PO)	Sulfamethoxazole/trimethoprim (PO)	Azithromycin (PO)	Amoxicillin/clavulanic acid (IV) Ceftriaxone (IV)
	1	0	Rifampicin (PO)	Doxycycline (PO)	Ethambutol (PO)	Metronidazole (PO) Moxifloxacin (PO)
	1	0	Sulfamethoxazole/trimethoprim (PO)	Ethambutol (PO)	Isoniazid (PO)	Rifampicin (PO) Piperacillin/tazobactam (IV)
	1	0	Colistin (IV)	Ethambutol (PO)	Ertapenem (IV)	Imipenem (IV) Moxifloxacin (PO)

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
	1	0	Rifampicin (PO)	Ethambutol (PO)	Moxifloxacin (PO)	Metronidazole (PO) Metronidazole (IV) Piperacillin/tazobactam (IV)
	1	0	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	Amikacin (IM)	Azithromycin (PO) Moxifloxacin (PO) Ethambutol (PO)
	1	0	Sulfamethoxazole/trimethoprim (PO)	Amoxicillin/clavulanic acid (IV)	Ethionamide (PO)	Pyrazinamide (PO) Kanamycin (IV) Moxifloxacin (PO) Terizidone (PO) Ethambutol (PO)
	1	0	Ethambutol (PO)	Ethionamide (PO)	Isoniazid (PO)	Pyrazinamide (PO) Metronidazole (PO) Linezolid (PO) Moxifloxacin (PO)
	0	1	Sulfamethoxazole/trimethoprim (PO)	Bedaquiline (PO)	Clofazimine (PO)	Pyrazinamide (PO) Levofloxacin (PO) Isoniazid (PO) Ethambutol (PO)
	0	1	Ethambutol (PO)	Bedaquiline (PO)	Clofazimine (PO)	Linezolid (PO) Levofloxacin (PO) Pyrazinamide (PO) Isoniazid (PO)
	1	0	Ethambutol (PO)	Ethionamide (PO)	Isoniazid (PO)	Pyrazinamide (PO) Moxifloxacin (PO) Kanamycin (IM) Terizidone (PO)
	1	0	Sulfamethoxazole/trimethoprim (PO)	Ethambutol (PO)	Isoniazid (PO)	Imipenem (IV) Moxifloxacin (PO)

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
						Rifampicin (PO) Metronidazole (PO)
	0	1	Ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Bedaquiline (PO)	Linezolid (PO) Levofloxacin (PO) Clofazimine (PO) Pyrazinamide (PO) Isoniazid (PO)
	1	0	Ethambutol (PO)	Azithromycin (PO)	Clindamycin (PO)	Ethionamide (PO) Moxifloxacin (PO) Pyrazinamide (PO) Kanamycin (IM) Terizidone (PO) Isoniazid (PO)
	0	1	Ethambutol (PO)	Bedaquiline (PO)	Ceftriaxone (IV)	Linezolid (PO) Levofloxacin (PO) Clofazimine (PO) Isoniazid (PO) Pyrazinamide (PO)
	1	0	Ethambutol (PO)	Amoxicillin/clavulanic acid (IV)	Ethionamide (PO)	Kanamycin (IM) Moxifloxacin (PO) Isoniazid (PO) Pyrazinamide (PO)
Paediatric ward	1	0	Amikacin (IV)	Vancomycin (IV)		
	8	11	Amikacin (IV)	Piperacillin/tazobactam (IV)		
	0	2	Amoxicillin/clavulanic acid (PO)	Vancomycin (IV)		
	2	1	Azithromycin (PO)	Ceftriaxone (IV)		
	1	4	Ampicillin (IV)	Cefotaxime (IV)		
	0	1	Amikacin (IV)	Cefotaxime (IV)		
	25	23	Ampicillin (IV)	Gentamycin (IV)		

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
	1	0	Amoxicillin/clavulanic acid (IV)	Azithromycin (PO)		
	1	0	Amoxicillin/clavulanic acid (PO)	Piperacillin/tazobactam (IV)		
	0	2	Amoxicillin/clavulanic acid (PO)	Ceftriaxone (IV)		
	0	1	Amoxicillin/clavulanic acid (IV)	Sulfamethoxazole/trimethoprim (IV)		
	0	2	Ampicillin (IV)	Ceftazidime (IV)		
	0	1	Ampicillin (IV)	Cefotaxime (IV)		
	0	1	Ceftazidime (IV)	Meropenem (IV)		
	0	1	Clindamycin (IV)	Cloxacillin (IV)		
	1	0	Cloxacillin (IV)	Meropenem (IV)		
	2	0	Cefotaxime (IV)	Cloxacillin (IV)		
	3	0	Cefotaxime (IV)	Sulfamethoxazole/trimethoprim (PO)		
	1	0	Cefotaxime (IV)	Vancomycin (IV)		
	2	2	Meropenem (IV)	Vancomycin (IV)		
	1	0	Rifampicin (PO)	Cefotaxime (IV)		
	2	0	Rifampicin/isoniazid (PO)	Pyrazinamide (PO)		
	1	0	Sulfamethoxazole/trimethoprim (PO)	Isoniazid (PO)		
	1	0	Amikacin (IV)	Piperacillin/tazobactam (IV)	Vancomycin (IV)	
	1	0	Ampicillin (IV)	Ceftriaxone (IV)	Gentamycin (IV)	
	0	1	Meropenem (IV)	Metronidazole (PO)	Piperacillin/tazobactam (IV)	
	1	0	Rifampicin/isoniazid (PO)	Pyrazinamide (PO)	Vancomycin (IV)	
	1	0	Rifampicin/isoniazid (PO)	Amoxicillin/clavulanic acid (IV)	Pyrazinamide (PO)	
	0	1	Rifampicin/isoniazid (PO)	Ethambutol (PO)	Pyrazinamide (PO)	
	0	1	Ampicillin (IV)	Amikacin (IV)	Gentamycin (IV)	
	1	0	Ampicillin (IV)	Cloxacillin (IV)	Gentamycin (IV)	
	3	1	Ampicillin (IV)	Azithromycin (PO)	Gentamycin (IV)	
	2	0	Sulfamethoxazole/trimethoprim (IV)	Gentamycin (IV)	Ampicillin (IV)	
	0	1	Ampicillin (IV)	Amoxicillin/clavulanic acid (IV)	Gentamycin (IV)	
	1	0	Amikacin (IV)	Ceftazidime (IV)	Cloxacillin (IV)	

Ward	Frequency in the pre-introduction period	Frequency in the post-introduction period	Antibiotic 1*	Antibiotic 2*	Antibiotic 3*	Antibiotic 4 and above*
	0	1	Ampicillin (IV)	Ceftazidime (IV)	Ceftriaxone (IV)	
	0	1	Sulfamethoxazole/trimethoprim (PO)	Gentamycin (IV)	Ampicillin (IV)	
	1	0	Ampicillin (IV)	Ceftriaxone (IV)	Gentamycin (IV)	
	1	0	Sulfamethoxazole/trimethoprim (PO)	Isoniazid (PO)	Ceftriaxone (IV)	
	0	1	Ceftriaxone (IV)	Sulfamethoxazole/trimethoprim (PO)	Gentamycin (IV)	
	1	0	Sulfamethoxazole/trimethoprim (IV)	Azithromycin (PO)	Gentamycin (IV)	Ampicillin (IV)
	0	1	Amikacin (IV)	Ampicillin (IV)	Gentamycin (IV)	Piperacillin/tazobactam (IV)
	0	1	Azithromycin (PO)	Cefotaxime (IV)	Gentamycin (IV)	Piperacillin/tazobactam (IV)
	1	0	Rifampicin/isoniazid (PO)	Ampicillin (IV)	Ethambutol (PO)	Pyrazinamide (PO)
	1	1	Rifampicin/isoniazid (PO)	Sulfamethoxazole/trimethoprim (PO)	Pyrazinamide (PO)	Ethambutol (PO)
	0	1	Rifampicin/isoniazid (PO)	Ceftriaxone (IV)	Flucloxacillin (IV)	Pyrazinamide (PO)

*IV: intravenous IM: intramuscular PO: by mouth