EVALUATION OF RATIONAL USE OF MEDICINES IN PUBLIC HEALTHCARE FACILITIES

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ABSTRACT

Background: Access to quality healthcare in South Africa is known to be unequal, with those who can afford it, receiving the best quality healthcare services in the private sector, and those who cannot afford it, having to receive healthcare in the public sector. The South African government is implementing the National Health Insurance to remove unequal access to healthcare services. However, the aim of this study is to evaluate the current usage of medicine.

Methodology: A quantitative, observational, descriptive, non-experimental, cross-sectional process of collecting data, using World Health Organization and International Network for Rational Use of Drugs (WHO/INRUD) core drug indicators from 20 public hospitals in the Limpopo Province, South Africa. Four (4) hospitals per district were randomly selected. The retrospective data, used for the prescribing indicators, included 30 randomly selected, out patients' files, from each hospital. Cross-sectional data were used for the facility indicators, collected from pharmacy managers in individual questionnaire. The index of rational drug prescribing (IRDP) and index of rational facility specific drug use (IRFSDU) was calculated for prescribing indicators and facility specific indicators, respectively. Retrospective data for rational antimicrobial indicators were collected from 10 inpatients, per facility, resulting 200 patient folders that were evaluated. The data was analysed using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 25.0, to obtain average and standard deviations, and presented in tables and figures.

Results: The average number of medications prescribed per encounter was 4.25 (*SD*= 0.69), with an IRDP of 0.44. The percentage of medicines prescribed by generic name was 43.78% (*SD* = 9.96), with an IRDP of 0.44. The percentage of antimicrobials prescribed was 28.17% (*SD* = 8.59), with an IRDP of 0.93. The percentage of injections was 8.33% (*SD* = 7.64), with an IRDP of 0.91. Finally, the percentage of medicine prescribed from the Essential medicines list (EML) was 92.46% (*SD* = 3.05), with an IRDP of 0.92. Regarding facility indicators, all facilities had functional Pharmacy and Therapeutics Committee (PTCs); however, not all had access to up-to-date medicine resources and hospital formularies. The total IRDP and IRFSDU was 3.64 and 4.05, respectively. The average hospital stay was 5.18 days (*SD = 1.7)*, the average number of antimicrobial prescribed per inpatient was 2.19 (*SD* = 0.32), and there was 33.3% cases of pneumonia, of which 65.57% were treated according to treatment guidelines. A microbiological investigation were evident in 16 cases. Antibiotics were prescribed by generic names in 33.33% (*SD* = 10.56) of cases, and from the EML in 100% (*SD* = 1.54) of cases.

Conclusion: Prescribing polypharmacy and not using generic names were factors that influenced the irrational use of medicine. There was a decrease in the percentage of antimicrobial and injections usage as compared to similar study primary healthcare (PHC) in South Africa; however, adherence to an antimicrobial guideline was still a challenge.

Recommendations: It recommended that PTCs be encouraged to perform evidence-based medicine utilization evaluations, and implement strategies to promote more rational use of medicine. In addition, there is an urgent need to establish, implement, and monitor antimicrobial stewardship programmes at facility level.

KEY WORDS

Antibiotics

Antimicrobial

Essential Medicine Use

Polypharmacy

Rational Medicine Use

Treatment Guideline

LIST OF ABBREVIATIONS AND ACRONYMS

ABC	ABC analysis
ADR	Adverse drug reaction
AMR	Antimicrobial resistance
AMP	Antimicrobial Stewardship Programme
AMS	Antimicrobial stewardship
CAP	Community acquired pneumonia
DDD	Defined daily dose
EML	Essential medicines list
HCAIs	Healthcare-associated infections
HIV	Human immunodeficiency virus
HPCSA	Health Professional Council of South Africa
ICU	Intensive care unit
IMS	Intercontinental Marketing Services
INN	International non-proprietary name
INRUD	International Network for Rational Use of Drugs
IPC	Infection Prevention and Control
IRDP	Index of rational drug prescribing
LOS	Length of stay
MDG	Millennium Development Goal
MUE	Medicine use evaluation

MRS	Medicine and related substance
NDP	National drug policy
NDoH	National Department of Health
PCDT	Primary care drug therapy
PHC	Primary health care
PPIs	Proton-pump inhibitors
PTC	Pharmacy and Therapeutics Committee
RMU	Rational medicine use
SAMF	South African medicine formulary
SAPC	South Africa Pharmacy Council
SSI	Surgical site infection
STG	Standard treatment guideline
TB	Tuberculosis
TOR	Terms of reference
VEN analysis	Vital, essential and non-essential analysis
WHO	World Health Organization

LIST OF DEFINITIONS

ABC analysis: Classification of inventory items into three categories (A, B, and C), according to the value of their annual usage, which is used to analyse medicine consumption and utilization, comparing actual versus planned purchases, justifying procurement budgets, guiding procurement patterns, and setting priorities for stock management.

Adverse drug reaction: Is a response to a medicine that is noxious and unintended, and which occurs in doses normally used in humans for the prophylaxis, treat of diseases, or for modification of physiological functions.

Antibiotic: Natural, semi-synthetic, or synthetic substance that is derived from other microorganisms. It may be bactericidal (kill bacteria) or bacteriostatic (inhibit bacterial growth).

Antimicrobial: A substance that may be natural, semi-synthetic, or synthetic, which could kill or inhibit the growth of microorganisms. These include antibiotics, antivirals, antifungals, antihelmithics, and antiprotozoals (RSA, NDoH, 2019).

Antimicrobial prophylaxis: Refers to the prevention of infection complication, using antimicrobial therapy.

Antimicrobial resistance: Is the resistance of microorganisms to antimicrobial agents, which happens when microorganisms change to protect themselves from antibiotics.

Consumption: The rate at which items are issued to clients or patients. This is also called demand. Consumption is usually measured in terms of units consumed within a specific period.

Hang-time: The time from prescription (be it handwritten or as part of an electronic order) of an intravenous antimicrobial to the time of infusion of said antimicrobial (RSA. NDoH, 2019).

Health literacy: Refers to an individual's capacity to obtain, process, and understand basic health information, as well as services needed to make appropriate health decisions (Martin et al, 2005).

Irrational prescribing: Refers to the medically inappropriate and economically ineffective use of pharmaceuticals.

Medication abuse: Describes a situation, when an individual uses medicines excessively, to the extent that it becomes harmful.

Medication misuse: Describes a situation, when someone does not use medication correctly.

Medicine promotion: All information and persuasive activities by manufacturers, distributors, to induce/influence the sale and use of medicine.

Medicine use evaluation: A system of ongoing, systematic, criteria-based evaluation of medicine use that helps to ensure the appropriate use of medicine, similar to drug utilization reviews.

Pharmaceutical care: Refers to an extended professional role, in which the pharmacist assumes responsibility for pharmaceutical and health outcomes (that impact on patient quality of life, for example, identifying and resolving medicine-related problems).

Pharmacovigilance: Is the science and activities concerned with the detection, assessment, understanding, and prevention, of adverse reactions to medicines.

Prescribing cascade: Occurs when patients take a medication, and suffer from some adverse drug reactions, which are misdiagnosed by the physician, as symptoms of diseases requiring more medication.

Quality: Is an optimal balance between possibilities realised and a framework of norms and values.

DECLARATION

I, Vutomi Valoyi, declare that:

- The research reported in this thesis is my original work, except where referenced.
- This thesis has not been submitted for any degree or examination at any other university.
- This thesis does not contain other persons' data, pictures, graphs, or other information, unless specifically acknowledged as being sourced from other persons.
- This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted:
    - their words have been re-written, but the general information attributed to them has been referenced:
    - and their exact words used, their writing has been placed inside quotation marks, and referenced.

Student: Vutomi Valoyi

Date: July 2020

Signature: ....

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I would like to acknowledge the hard work and dedication shown by Vutomi in completing this research project and final thesis. Vutomi passed away before he could receive the degree, a Masters in Pharmacy. I would like to extend my condolences to the family, friends and colleagues. Vutomi was a young and vibrant pharmacist who applied his knowledge and skills in his work. His research project contributed to the work around rational use of medicines in the Limpopo Province. He will be missed.

May he rest in peace.

Prof Coetzee

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CHAPTER ONE

INTRODUCTION

1.1. Background to study

The aim of any health care system is to provide the correct medicine to patients, who need it (Arora, Sachdeva, & Kumari, 2017). The important component of an efficient healthcare system is access to affordable, quality, safe, and effective medicine (Ojo, Igwilo, & Emedoh, 2014). Ensuring the availability of adequate quality, as well as quantities of pharmaceuticals, has been the principal concern in the last decades; however, currently, with the improved availability of pharmaceuticals in developing countries, promoting their use has become a greater concern (Abdelgadir & Elkhwad, 2014). The World Health Organization (WHO) developed the concept of essential medicine, intended to meet the health needs of the majority of the population; however, about one third of world's population lack access to these essential medicines, and those who have access, are given the incorrect medication, too little medicine for their ailments, or do not use the medication correctly (Afriyie & Tetteh, 2014; Desalegn, 2013).

Medicines are administered to achieve a definite outcome that would improve the patient's quality of life, including alleviating the symptoms of the disease, slowing the progress of the disease, curing, as well as preventing the disease (Hepler & Strand, 1990). However, these medicines are often used irrationally, which places these advances in jeopardy, threatens future health gain, and wastes scarce resources (Systems for Improved Access to Pharmaceuticals and Services [SIAPS] Program, 2015). Many documented research studies have described medicine use in developing countries as irrational; the prescribing and use of ineffective, suboptimal, unsuitable, or unsafe pharmaceutical products (Smith, 2004). It is estimated that, worldwide, more that 50% of medicines are prescribed, dispensed, or sold inappropriately, while 50% of the patients fail to take them correctly (World Health Organization [WHO], 2002). The quantities of medicines prescribed for a particular illness, are often far more than reasonably required (World Health Organization [WHO], 2006). Worldwide, rational medicine use (RMU) is acknowledged as an important part of the health management system that should to be improved to benefit patient welfare, and the community economy (Amin, Khan, Azam,

& Haroon, 2011), as well as optimize the quality of healthcare delivery (Ofori-Asenso, Brhlikova, & Pollock, 2016). At a WHO conference, held in Nairobi, in November 1985, rational medicine use was defined as the need for patients to receive medication, appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time, as well as at the lowest cost to them and their community (World Health Organization [WHO], 1987).

Afriyie & Tetteh (2014) view irrational medicine use as a common problem that deteriorates in developing countries, due to inadequate funds for medicine procurement, inadequate training of prescribers, the attitude of prescribers, and the patients' beliefs. Irrational medicine use may originate from inappropriate prescribing [inappropriate regimen]; inappropriate delivery [unavailability of medicine due to economic barriers and sociological barriers]; inappropriate formulations, dispensing errors [incorrect or inadequately labelled, insufficient patient advice and information], inappropriate behaviour by the patients [compliance with inappropriate regimen, or non-compliance with appropriate regimen], inappropriate monitoring [failure to monitor patient's outcome, detect and resolve inappropriate therapy] (Hepler & Strand, 1990). Many studies reveal that the most common types of irrational use of medicine includes: the patients' usage of too many medicines (poly-pharmacy); the use of antimicrobial, while not indicated; inadequate dosage of antibiotics; over use of injections, when oral formulations would be more appropriate; failure to prescribe, in accordance with standard treatment guidelines (STG); and irrational self-medication of medicines, frequently taken in under-doses (World Health Organization [WHO], 2010; Akl, El Mahalli, Elkahky, & Salem, 2014; Hogerzeil, 1995). Apparently, the high percentage of injections, as well as antibiotic prescribing, was due to disease burden, a weak health system, and the patients' preference (Ofori-Asenso et al., 2016).

Promoting RMU for all medical conditions is essential, in the provision of universal access to adequate healthcare, satisfaction of health-related human rights, as well as the achievement of health Millennium Development Goals [MDG] (El Mahali et al., 2012). To address the irrational use of medicines; prescribing, dispensing, and the patients' compliance, should be monitored regularly, based on the type, amount of irrational use, and the reasons for irrational medicine use, to develop a strategy that focuses on particular problems, and measures the impact of such a strategy (WHO, 2002). The WHO, in collaboration with International

Network for Rational Use of Drugs (INRUD), has developed core drug-use indicators in three related areas, namely, prescribing, patient-care, and facility specific factors, for use in any country, facility, or region, to measure medicine use, and promote RMU (Chapagain, Pokharel, & Paranjape, 2016).

There are four main methods that should be used regularly to promote RMU. Firstly, the *aggregated data method* comprises data not relating to an individual patient only, and identifies broad problem areas, for example, the ABC analysis, Vital, Essential and Non-essential (VEN) analysis, and Defined Daily Doses (DDD). Secondly, *qualitative methods*, such as the structured questionnaire, and in-depth interview, which provide explanations for the occurrence of problems. The third method is *medicine use evaluation* (MUE), which audits medicine usage and provides feedback. The fourth method is the *medicine 'drug' indicator method*, which involves collecting data from individual patients; however, this method does not provide enough information to assess the appropriateness of the diagnosis (Holloway & Green, 2003).

Medicines should always be used rationally, to maximize therapeutic outcomes, reduce medicines interactions and adverse drug reactions (ADRs), shorten hospital length of stays [LOS], as well as reduce healthcare cost for patients and settings (Sisay et al., 2017). Promoting RMU could improve the quality of, and accessibility to, medicine, facilitating improved quality of life for the community (Sabir, 2018). Therefore, the researcher is of the opinion that each health facility needs to evaluate its own medicine usage, regularly, in order to identify areas that need improvement, and ensure the safe and effective use of medicine.

1.2. Problem Statement

The most cost-effective medical intervention for saving lives and improving health, is essential medicines, which constitute 20-40% of the health budget in many developing countries (Management Sciences for Health [MSH], 2012). However, when essential medicines are used inappropriately, increased costs and the lack of resources ensue, leaving the public healthcare system incapacitated to procure sufficient medicines to meet patient demand (MSH, 2012). Therefore, the researcher is of the opinion that despite the interventions of the South African Government to improve safe and effective use of medicines, inappropriate medicine use remains a challenge. Pharmaceuticals in South Africa, public sector are one of main cost drivers following salaries.The National Health Insurance (NHI) is being introduced in South Africa, to ensure that every citizen receives the best, cost-effective treatment; therefore, it is important to evaluate the current medicine use at health facility level.

1.3 Research setting

The study was conducted at 20 public healthcare facilities in the Limpopo Province, including district, as well as regional hospitals, which were conveniently selected.

1.4. Research question

The following is the main research question of this current study, "Are medicines being used rationally in public healthcare facilities in the Limpopo Province?"

1.5. Research Design

The research design employed in this current study was an empirical, non-experimental, quantitative, observational, descriptive, cross-sectional research design, collecting retrospective data from aggregate data sources, namely, existing medical data records, as well as structured individual interviews with a pharmacist at each of the 20 selected public healthcare facilities for facility indicators. Prescribing indicators and antimicrobial indicators were evaluated for out-patients and in-patients, respectively. WHO/INRUD validated standardized tools were adopted to produce the data collection forms to collect core drug use indicators, to be compared with other studies across the world. The study consisted of a literature review and an empirical investigation.

1.6. Research Aim

The main aim of the study was to investigate whether medicines were being used rationally at public health care facilities in the Limpopo Province.

1.7. Research objectives

The main objectives of this study were to:

1. Conducted a literature review on the rational use of medicines.
2. Described the use of medicines at public sector health facilities.

3. Reported on the findings of this current study.

Specific research objectives: Literature review:

- Reviewed irrational use of medicines around the world.
- Reported on the consequences of irrational medicine use.
- Described interventions to improve rational use of medicines.
- Described the role of pharmacist/pharmacist student in improving rational medicine use.
- Reviewed current literature for educational outcomes related to medicine utilization evaluation.

Specific research objectives: Empirical investigation:

- Identified and described medicine use problems by using the WHO/INDRUD indicator tools.
- Evaluated quality of patient's care by using rational antimicrobial use indicator tools Evaluated the use of antibiotics in the hospital at baseline to inform facility's antibiotic stewardship programs.
- To make policy recommendations to improve the prescribing of medicines.

1.8. Significance of the study

The NHI will be limited to prescribed services, which will include a medicine formulary; therefore, it is imperative to evaluate prescribers' current adherence to standard treatment guidelines, as well as identify where the irrational use of medicine challenges emanate from. The results of this current study would identify areas of improvement, to ensure safe use of medicines.

1.9. Limitations and scope of the study

The objective of this current study was to describe the medicine use problem by prescribers using WHO/INRUD indicator; however, it failed to consider that the prescriber's decision might have been influenced by patients' demands. This current study did not include patient care indicators to determine the quality of healthcare, as only patients can determine the quality of service delivered. In addition, the sample size of the antimicrobial indicators, to evaluate the rational use of medicine to admitted patients, was too small to form a reproducible conclusion.

1.10. Structure of the study

- Chapter One comprises the background to the research study, as well as the problem statement, research setting, research question, research design, research aim and objectives, significance, as well as the limitations and scope of the study.
- Chapter Two contains a detailed literature review.
- Chapter Three encompasses the methodology that was followed, as well as the ethical considerations applied in this research study.
- Chapter Four comprises the results obtained during the research study.
- Chapter Five incorporates a discussion of the results obtained, as well as the limitations of the study.
- Chapter Six includes the conclusions, recommendations and recommendations for future research.

CHAPTER TWO

LITERATURE REVIEW

2.1. Introduction

The researcher conducted a literature review, using appropriate databases such as, EBSCOhost, Google Scholar, ScienceDirect and PubMed. The relevant literature was identified by using the following key words: rational medicine use; irrational medicine use; impact of irrational medicine use; polypharmacy; antimicrobial resistance; intervention to improve rational medicine use; role of pharmacist; role of clinical pharmacist; and medicine utilisation review. Only publications published in English, between 1998 and 2020, were included in the review.

2.2. Review on the irrational use of medicine around the world

Poor or weak implementation of the National Drug Policy (NDP), lack of communication between healthcare providers and patients, short consultation times, traditional beliefs of illness, poor knowledge of healthcare providers, and the short years of service, are some of the factors associated with irrational medicine use (Ojo et al., 2014). The lack of man-power to regulate irrational medicine use; policies that were supposed to be implemented in facilities, which were not strictly implemented; and no penalties for irrational prescribing are some of the barriers to the promotion of rational medicine use (Chandy, 2008). However, it has been observed that more than 50% of all countries fail to implement basic policies to promote the rational use of medicine (WHO, 2010).

Irrational prescribing is one of the practices that leads to irrational medicine use, and is regarded as a *disease* which is difficult to *cure*; however, prevention is always possible (Arshad et al., 2016). Although *irrational prescribing* is not a new global phenomenon, and has been a worldwide concern for years, many countries still do not pay the necessary attention to this continuous challenge (Hashemi, Nasrollah, & Rajabi, 2013). According to Atif et al. (2016), prescription is a reflection of the country's healthcare system and prescribers' attitude toward the disease treated. Several factors influence the prescribers when they decide on the best treatment option, which includes their conception of the disease, the information to which they have access, the sociocultural and economics of the population, the availability of medicine in the facility, as well as pressure from pharmaceutical representatives (Dos Santos, Ottati, & Nitrini, 2004). Irrational prescribing could be affected by the lack of up-to-date, evidence-based medicine information, continuous in-service training, poor supervising systems, as well as the patients' demands (MSH, 2012). In addition, a shortage of human resources could lead to health professionals being compelled to fulfil both the roles of prescribing, as well as dispensing, which breeds irrational prescribing, as there is no mechanism in place to detect incorrect, or poor prescribing. An example appears to be dispensing doctors in Zimbabwe, who were observed to prescribe more antibiotics, than their non-dispensing counterparts (Ofori-Asenso et al., 2016).

"Poor access to unbiased medical information, national standard treatment guideline (STG) may result in same medical condition being treated with different treatment which may not be the optimal" (Green, Omari, Siddiqui, Anwari, & Noorzaee, 2010, p. 23). Medicine promotion could trigger increased advertisement-induced patient demands, and/or the prescriber's decision could be influenced by incomplete information, leading to irrational prescribing (Edrees & Elkwad, 2010). The more accessible medicines are to patients, the more likely they are to adhere to their medication, and consequently, their health will improve, as well as trust in the health system (Abdulah et al., 2014). In 1993, the average amount of medicine per encounter, in Sudan's rural facilities, was 0.9; not because of rational prescribing, but instead, the poor supply system of medicine; however, by the time the supply of medicine was improved, the figure rose to 1.2 (Hogerzeil et al., 1993). Therefore, it is evident that the increased availability of, and accessibility to medicine, triggers increased access to the medicine that patients received.

Patient encounter refers to the interaction between a prescriber and a patient, which includes history-taking, diagnoses process, selection of therapy (pharmacological and non-pharmacological), advice on treatment (including their adverse drug reaction [ADR]), follow-up and prevention (Ofori-Asenso et al., 2016). Patient load, however, is known to promote irrational prescribing practices (Ahiabu, Tersbøl, Biritwum, Bygbjerg, & Magnussen, 2016), as the duration of patient encounter tend to be shorter. However, the key aspect of quality healthcare is determined by the patients' satisfaction. Wathoni & Rahayu (2014) assert that there is a strong relationship between communication and the patient's satisfaction. The length of time that patients spend with prescribers, significantly influences their satisfaction with the health service provided, as well as their adherence to the treatment (Afriyie & Tetteh, 2014). Patients, frequently, fail to follow their treatment regimen correctly, due to incorrect, or insufficient medicine information received, for example, they may swallow a chewable or sublingual tablet (Arora et al., 2017).

Prescribers with fewer years of clinical experience are more likely to prescribe polypharmacy (Ojo et al., 2014), while patients prefer those who prescribe more medicines, as they believe it will ensure improvement, and cure their condition faster (Bashrahil, 2010). Most researchers have observed that the number (percentage) of patients, who remember their dosing schedules, decreases, when an increased amount of medicine is prescribed (Ofori-Asenso et al., 2016). The direct correlation between the number of medicines prescribed and occurrence of ADR has been revealed in a study conducted in South Africa by Ofori-Asenso et al. (2016), while polypharmacy increases the risk of medicine reactions, and creates cycle of health demands and costs, as new treatment would be required (ibid).

The time the pharmacist spends with the patient, explaining how the medication should be used, as well as the quality of the labelled medication, could affect the patient's compliance (El Mahalli et al., 2012). If the medicines are inadequately labelled, and/or insufficient medicine information is provided, then prescribing correctly does not guarantee that the medicines will be taken as intended (Le Grand, Hogerzeil, & Haaijer-Ruskamp, 1999). The WHO recommends that the patient's label must display the medicine regimen, dose, and patient's name (Abdulah et al., 2014). According to South Africa, Medicine and Related substance Act 101 of 1965, regulation 8(5) as amended, dispensed medicine must have proprietary name, name of a patient, direction on how medicine how medicine must be used, name and address of the dispenser, dispensing date, and reference number on the label. The dispensing time, as a process indicator, is less important than the output indicator, such as adequate labelling and the patients' treatment knowledge (Hogerzeil et al., 1993). In Serbia, pharmacist in public sector usual earn less and there is poor communication between pharmacist and prescribers in everyday practice, the two could influence the pharmacist's motivation, as well as the quality of the pharmaceutical service (Prokic, Davidovic, & Gunjic, 2014).

The patients' demand for antibiotics also plays a huge role in irrational prescribing of antibiotics, especially in the private sector, because of the prescriber's fear of losing customers (Ofori-Asenso et al., 2016). In addition, there are many common cultural beliefs about medicine among patients, including, antibiotics can treat many illnesses, injections are more powerful than pills, and there is a pill for every symptom (Bbosa et al., 2014). In 1993, it was observed in Ghana that the level of education (including health literacy), religious background, as well as location of residence, were important factors, which influenced the utilization of maternal and child healthcare in rural areas (Smith, 2004). In addition, poorer households spent a higher proportion of their income on healthcare, compared to more affluent households (ibid). Community health awareness, therefore, plays a role in the improvement of rational medicine use (RMU), as well as other health services.

India has many pharmaceutical companies that manufacture generic products under different brands names. This results in increased competition, prompting companies to encourage prescribers to prescribe *their* brand names, in exchange for incentives, which leads to medicines being prescribed without indication, and in irrational combinations (Aravamunthan, Arputhavanan, Subramaniam, & Udaya Chander, 2017). The average medicine per patient encounter in India was 3.7, and the percentage of medicine prescribed by generic name, was 2.5% (Aravamunthan et al., 2017), which indicates how influential pharmaceutical companies are in promoting irrational medicine use.

The unavailability of an essential medicine list (EML) and standard treatment guidelines (STGs), are also perceived as barriers for prescribers to prescribe, in accordance with STGs; however, where they were available, staff members, reportedly, were afraid to use them in the presence of patients, for fear of losing the patient's faith in them (Orrell & Kishuna, 1997). This implies that the availability of reference books and standard guidelines does not guarantee their effective use.

Antimicrobial medicine is considered one of the pillars of modern medicine; however, antimicrobial resistance (AMR) appears to be emerging faster than the development of new antimicrobial medicine, which is a major public health threat (Truter, 2015). This common challenge could lead to irrational antibiotic prescribing, the use of the incorrect combination of antibiotics, failure to adhere to local or international guidelines, incorrect agent of choice, and (after obtaining laboratory confirmation) the failure to de-escalate or escalate to a narrow spectrum agent, as well as the unnecessary, prolonged, duration of therapy (Lim et al., 2015). Researchers observed a direct correlation between antibiotic use and resistance development (Ahiabu et al., 2016). Evidently, the emergence of antimicrobial resistance cannot be prevented; but, its prevalence can be reduced (Hashemi et al., 2013).

The emergence of AMR in developing countries is common, and increasing, most likely due to high infectious disease burden, limited access to quality assured antimicrobial medicine in the country, the lack of diagnostic tools, as well as laboratory facilities to help prescribers to narrow their suspicions and arrive at definite diagnoses (Ahiabu et al., 2016), which may promote the use of antibiotics combinations and defensive (broad-spectrum) medicines (Chandy, 2008). The lack of diagnostic tools may also lead to imprecise diagnoses, due to the overlapping clinical features of viral and bacterial infection (Brink et al., 2016). Some prescribers determine the duration of treatment, based on what they are familiar with, instead of following evidence-based research, or national guidelines (Mendelson, 2015). While on the other hand, time-constraints to perform full clinical assessments, as well as their denial of the negative impact of over-prescribing antibiotics (Brink et al., 2016), also influence their decisions.

Increasing irrational antibiotic use is reported with common examples, such as inappropriate prolonged antimicrobial prophylactic duration (lasting up to a month), empirical antibiotic prescribing, which is associated to limited access to diagnostic facilities, due to budget constraints, and often, the lack of facilities in rural areas (Irunde, Minzi, & Moshir, 2017). Additionally, often the shortage of antibiotics leads to premature changes, or discontinuance, the clinical guidelines are unavailable, and in some provinces the Pharmacy and Therapeutics Committee (PTC), also known as Drug and Therapeutics Committee (DTC), are reportedly dysfunctional (Republic of South Africa [RSA], National Department of Health [NDoH], 2007). Irrational antibiotic use also occurs when local epidemiological and antibiotic susceptibility are not considered, when antibiotics are prescribed to treat colonisation, instead of invasive infection, or the excessive use of antibiotics for inappropriate surgical prophylaxis. Currently, a shorter duration of therapy is recommended, as longer durations may predispose the patient to infection with more resistant organisms, and there is no evidence to suggest that the combination of antibiotics increases efficacy, or decreases resistance (Brink et al., 2006). Besides, when patients fail to complete the course, or skip doses (intentionally or forget), some re-use the leftovers, which may result in the failure to eradicate the microbial infection, or cause ADR (Bbosa et al., 2014). Therefore, proper medicine disposal also merits attention, especially for antibiotics, as improper methods of disposal may allow it to enter into the water system, resulting in further exposure and resistance (Chandy, 2008).

Injectable drugs are expensive, and excessive use of them may have negative consequences, such as anaphylactic shock, tissue necrosis, and the transmission of blood borne infections, for example, HIV, and hepatitis (Smith, 2004). Although injections are more costly than oral formulations, there are limited alternative modes for young children, and are the parents' preference; therefore, the increased use of injections (Atif et al., 2016).

2.3. Report on the consequences of irrational medicine use

The impact of irrational medicine use may yield diverse consequences, including the reduced quality of therapy (resulting in increased morbidity and mortality), bacterial resistance and ADRs, as well as a waste of limited resources (leading to reduced resource availability and increased cost), and psychosocial effects, such as patients becoming over-dependent on medicines (Sabir, 2018). Desalegn (2013) observed that new graduates would often imitate the prescribing habits of their seniors, maintaining the vicious circle, and making it difficult to change the existing prescribing habit, which leads to prolongation of illnesses, increased hospital length of stay [LOS], harm to the patients, and increased healthcare costs. Irrational medicine use may also result in increased hospital return visits, which creates psychosocial problems for patients and their families (Bbosa et al., 2014). Inappropriate prescribing contributes directly, or indirectly, to the patient's reliance on medicine, which may increase the patients' demand (MSH, 2002), and lead to reduced access to medicine, resulting in decreased attendance rates, due to stock out, and the loss confidence in the health system (WHO, 2002).

Whenever a medical decision has to be made, safety issues arise (Alomar, 2014). The most reported adverse impact of irrational medicine use is ADR, which may result in harm to the patient (Sabir, 2018). ADR is one of the leading causes of morbidity and mortality in the world, which may affect hospital LOS, and, in turn, increase healthcare costs, as well as reduce the patient's productivity (Alomar, 2014). China has reported that approximately 2.5 million in-patients are admitted due to ADR, and about 60% of children, who are hearing and speech impaired, have originated from irrational use of medicine (Dong, Yan, & Wang, 2011). In 1994, it was reported by the American pharmaceutical system that in the past four decades, 106 000 people had died as a result of ADR. Again in 2000, it was reported by the Institute of Medicine in USA that between 44 000 and 98 000 deaths occurred annually, as result of medical error, which indicated an increase in death and morbidity from ADRs (Alomar, 2014). However, this study was criticised because the death rate was extrapolated from admission rates in 1994, yet based on rates of ADRs, taken from studies conducted before 1981 (Pirmohamed et al., 2004). In Africa, hospital admissions, and hospital admissions as a result of an ADR, is reportedly 8.4% and 2.8%, respectively; however, the report proportion is 0.9%, which indicates a low reporting rate in African countries (Barry et al., 2020). In addition, it appears that the number of reports submitted to the Food and Drug Administration (FDA) may only be a small percentage of the true ADR occurrence, while the treatment costs, due to ADR, is estimated at US$7 billion, annually (Waller & Harrison-Woolrych, 2017).

Poor quality medicines may result in ADR and treatment failure. In South Africa, counterfeit medicines are a challenge, as an estimated one-in-five medicines sold are believed to be counterfeit (Essack et al., 2011). The South African National Department of Health [NDoH] established the Pharmacovigilance cluster on national, and facility levels, to improve detection, prevention, and spontaneous reporting of ADR (Mehta et al., 2017).

When polypharmacy is prescribed, the increased chances of medicine interactions could lead to treatment failure and ADRs, which may result in a change of therapy, and consequently, increased costs (Irunde et al., 2017). Multiple medications not only add to the complexity of therapy, as well as the costs, but also places a patient at high risk of ADR and medicine interactions (Eze Uchenna & Odunayo Oluwakeni, 2010). Polypharmacy might emerge as a result of financial incentives to prescribers, as well as a shortage of therapeutically correct medicine (Atif et al., 2016).

In most medical conditions, accurate diagnoses and appropriate treatment are essential for the patients' survival and improved quality of life; however, the patients' failure to follow medical recommendations is a major barrier to effective treatment (Martin, Williams, Haskard, & DiMatteo, 2005). Patients may fail to adhere to instructions offered by healthcare providers, because of ignorance, misunderstanding the instructions, incorrect advice was provided, or the information was forgotten (Martin et al., 2005). Consequently, the patients' non-adherence to treatment may result in hospitalisation, regimen failure (for example in tuberculosis [TB] and HIV/AIDS cases), unnecessary changes to dosages (and therefore, increased healthcare costs), as well as the wasted time and energy of both the patients and the prescribers (Martin et al., 2005, p. 190). The patients' health literacy is central to their ability to adhere, as, firstly, they have to understand what they are expected to do, before they would be able to follow the provider's instructions (Martin et al., 2005). Ultimately, the morbidity and mortality associated with chronic diseases, such as cardiovascular, neurological, and asthma, may increase, due to the irrational use of medicine (Atif et al., 2016).

Healthcare-associated infections [HCAIs] are some of the most leading causes of morbidity and mortality. Patients usually have to remain in hospital for longer periods, require additional medical intervention, and therefore, subjected to increased health care expenditure (Napolitano, Izzo, Di Giuseppe, Angelillo, & the Collaborative Working Group, 2013). In South Africa, one-in-seven patients entering hospital are at risk of acquiring HCAIs (Brink et al., 2006).

The irrational use of antimicrobial medicine is of serious concern, because it could result in the development of AMR, which is spreading worldwide (Holloway, 2011), complicating the treatment of common infectious diseases, and creating increased healthcare costs. Patients from poor backgrounds are mostly the ones affected by the rapid rise of AMR; however, they may not be able to afford the antibiotics (Chandy, 2008). In addition, the inappropriate use of antibiotics in surgical prophylaxis could result in increased incidences of surgical site infections [SSIs], leading to increased healthcare costs, which includes medicines, the nurses administering it, and medical supplies, subsequently, causing ADR and AMR (Green et al., 2009). Currently, it is estimated that, globally, 70 000 people die every year. This is expected to escalate to 10 million deaths, annually, if no international action is taken by 2050, and at a cumulative cost of 100 trillion US dollars, globally (Brink et al., 2016). Approximately 70% of the patients with illnesses, such as acute diarrhoea, which commonly is a viral aetiology, are treated with antibiotics (Chandy, 2008). There is increased use of empirical antibiotics in Tanzania, which is also known for a high burden of infectious diseases, as well as limited diagnostic facilities. However, antibiotics, such as ciprofloxacin, could be obtained over-the-counter, and 30-35% of medicines stores sell incomplete doses (Irunde et al., 2017). In Nigeria, with inadequate regulation for the distribution and sale of prescription medicine, antibiotics are obtained illegally, without prescription, ciprofloxacillin being the most used/purchased (Akinyadenu & Akinyadenu, 2014). Patients, who are infected with resistant microorganisms, are at higher risk of poor clinical outcomes, including mortality, as well as increased hospital LOS, and consume more healthcare resources, compared with those infected with antimicrobial sensitive microorganisms (Gasson Blockman, & Willems, 2018; Mendelson, 2015).

Self-medication is a major form of self-care; however, problems arise when people consider that for every sickness, or discomfort, medicine should be used. This has emerged as one of the contributing factors to emerging AMR, causing the delay of diagnoses, as well as delivery of effective treatment, and could lead to medicine misuse (Akinyadenu & Akinyadenu, 2014). A study conducted at Tygerberg Academic Hospital, in Cape Town, South Africa, revealed that most patients, who overdose on medicines, end up in the intensive care unit (ICU), with an average hospital stay of 4.7 days (Koegelenberg, Joubert, & Irusen, 2012).

Occasionally, medication is used for recreational purposes. Meel and Essop (2018) observed that infective endocarditis, due to the intravenous use of nyaope (mixture of heroin, cocaine and antiretroviral medicines), was responsible for the increased mortality and morbidity in predominantly young males in South Africa. The use of antibiotics by farmers for agriculture and animal growth, could lead to cross-resistance for humans, since, in practice, antibiotics are used for animal husbandry and agriculture (Chandy, 2008). Whereas more interventional studies in antimicrobial use are conducted in medical practice and facilities, none are performed in veterinary practice and agriculture (Bbosa et al., 2014).

The full impact of AMR on health economy and clinical outcomes is still unknown in South Africa (Truter, 2015). A study conducted in Cape Town, South Africa, revealed that the common causes of the irrational prescribing of antibiotics included, making no specific diagnosis, choosing the wrong antibiotic, issuing the incorrect dosage and duration, and prescribing antibiotics without indication (Gasson et al., 2018). It is estimated that in the post-antibiotic era, infectious diseases will become untreatable (Gasson et al., 2018). The pressure by pharmaceutical representatives to use broad-spectrum antibiotics, has contributed to this current situation (Ramsamy, Muckart, & Han, 2013). Currently, pharmaceutical companies are concentrating their research and medicine development on chronic illness, and not on antibiotics, because they are used for fixed duration and resistance issue, which leads to serious disastrous consequences, as the older antibiotics are being phased out, without replacements. In addition, pharmaceutical companies are advocating the irrational use of expensive and reserve antibiotics, through medical promotion (Chandy, 2008).

Excessive and irrational prescribing, as well as use of antibiotics remain important contributing factors to the emergence of AMR, such as multidrug resistance [MDR], extreme drug resistance [XDR], and pan-drug resistance [PDR], which is on the increase in South Africa (Brink et al., 2016). In South Africa, 80% of the antibiotics are prescribed in primary healthcare [PHC], with lower respiratory tract infection [LRTI] being the most frequent indication; however, the main concern is that some common infections are becoming difficult to treat (Truter, 2015; Brink et al., 2016). There is also an indiscriminate use of antibiotics in intensive care units [ICUs] in South Africa, due to the fear of selecting an incorrect antimicrobial to treat nosocomial infection, as it may result in therapeutic failure, and/or increased mortality rate; therefore, it is important to have an antimicrobial stewardship programme [ASP], especially in areas with frequent antimicrobial use (Ramsamy et al., 2013). Class restriction, and antimicrobial cyclic, are the proposed strategies to arrest the spread of AMR; however, over time it has exhibited increased resistance to alternative medicine (Ramsamy et al., 2013).

2.4. Describe interventions to improve the rational use of medicines

The WHO, government, and pharmacists have a critical role to fulfil in strategies to promote rational medicine use [RMU] (Sabir, 2018). The WHO developed a 12-core intervention to facilitate the appropriate medicine use, which includes: f*ormation of mandated multi-disciplinary national body to coordinate medicine use policies*; *clinical guidelines*; *essential medicines list, based on treatments of choice*; *drugs and therapeutics committees [DTC] in districts and hospitals*; *problem-based pharmacotherapy training in undergraduate curricula*; *continuing in-service medical education as a licensure requirement*; *supervision, audit and feedback*; *independent information on medicines*; *public education about medicines*; *avoidance of perverse financial incentives*; *appropriate and enforced regulation*; and *sufficient government expenditure to ensure availability of medicines and staff* (WHO, 2002). The government's responsibilities in the promotion of RMU, is the institution of a national drug policy [NDP], and the implementation of medicine programmes, as well as the monitoring thereof, to ensure that they are practiced by all health professionals. Additionally, the responsibility of the pharmacists, primarily, is lodged in patient counselling (Sabir, 2018, more details in section 3.4). According to the WHO, in many developing countries, efforts to promote RMU are poor, or non-existent (Ojo et al., 2014). Patterns of medicine prescribing, and use, have been studied in many countries; however, to date, no published overview, regarding the impact of an intervention/(s) to change medicine prescribing and use, exists (Le Grand et al., 1999). Rational prescribing dictates that the fewest medicines be used to achieve the therapeutic goal, as determined by the prescriber and the patient (Eze Uchenna & Odunayo Oluwakeni, 2010). Good prescribing practices require a professional collaboration between prescribers and the pharmacists, to serve the patients. Consequently, this would guarantee the safer use of medicines, to achieve the best health outcome for the patient (Abdulah et al., 2014).

Unrestricted availability of medicine, as in India, with more than 70 000 formulations (Santos & Nitrini, 2004), also contributes to irrational prescribing. The WHO introduced the concept of the essential medicine list [EML] in 1970, anticipating that fewer available medicines would enhance the long term, efficient supply of medicines, as well as sustainable access to medicine, better prescribing, and decreased healthcare costs; however, to date the prescribing practice is not improving and healthcare costs are escalating (WHO, 2010). In South Africa, private sector, prescribing is unrestricted, allowing the prescribers to select whichever antibiotics they consider most clinically appropriate (Chunnilall, Peer, Naidoo, & Essack, 2015), resulting in the prescription of more expensive antibiotics by dispensing doctors, and encouraging the influence of pharmaceutical representatives. The EML concept has improved access to medicines in many countries; however, its effect on the prudent use of medicines, is still unclear (Ahiabu et al., 2016).

The development of the STG, with wide consultation and consensus, properly launched with possible feed-back, face to face education focused on individual prescribing problems, automated order form, as well as focused educational campaigns and media, are proven, effective interventions, to promote RMU (Hogerzeil, 1995). Printed materials, solely (for example, Bullentin), are ineffective (MSH, 2012), as they are merely disseminated to healthcare providers, without a formal launch or introduction, and follow-up, especially when the prescribers were not involved in the development process (Hogerzeil, 1995). In the development of the STG and the EML process, manufacturers should not be involved, to prevent competing conflict of interest (Laing, Hogerzeil, & Ross-Degnan, 2001). The STG and EML are critical aspects of the South African National Health Policy, which serve to address the medicine availability and accessibility. Medicines in the EML are limited through criterion-based selection, in generic names, as well as stratified on primary and hospital-levels, and further stratified by guidelines for adults and paediatric patients; however, those medicines that are not included, may be requested for specific patients through a standardized process (Essack et al., 2011).

As for antibiotics, their inclusion or exclusion is guided by the microbial aetiology of the disease and the incidence of resistance; however, in South Africa, the latter has not played a role in the development of the STG and EML (Essack et al., 2011). According to Bonello and Stafrace (2016), prescribers are more likely to adhere to local guidelines, than international ones, as local guidelines take into consideration local AMR patterns, and therefore, are more effective in preventing infection and complications. South Africa, for example, represents a unique environment with a high prevalence of HIV, as well as AMR; therefore, guidelines must be locally applicable (Boyles et al., 2017). Only 9.3% of prescribers in Europe appeared to adhere to local guidelines, completely (Bonello & Stafrace, 2016). Prescribing in the public sector is guided by the STGs, a formulary, and the availability of medicines on the EML, which guidelines are available, electronically, in South Africa (Schellack et al., 2017). However, the implementation of the formulary system is ineffective, reportedly, and starts at medical organizations, as formularies are poorly disseminated to all healthcare organisations, and standardised criteria for medicine inclusion is lacking in the formulary (Rostova & Odegova, 2012).

From good diagnosis to rational prescribing, several factors affect the improvement of therapy; however, in medical therapy, the real determinant is the patient (Celik, Nazh, & Clark, 2013). Although healthcare providers fulfil a crucial role in the use of medicine, patients are equally important (Abdo-Rabbo, Al-Ansari, Gunn, & Suleiman, 2009). Irrational prescribing practices will not improve without consumer targeted interventions, which will educate and empower the public regarding the consequences of the inappropriate use of medicines (Aslam, Bushra, & Khan, 2012). Patients are known to equate the quality of healthcare service received with the medicine prescribed to them, such as the quantity, rather than the service itself (Ahiabu et al., 2016).

In many countries, policy makers and pharmacy representatives sought to promote a patient-centred healthcare and advisory service, to optimize the patient's use of medicine (Latif, Boardman, & Pollock, 2013). The co-payment for antibiotic use, imposed by the National Health Insurance (NHI) of Ghana, did not result in the decreased use of antibiotics, but a decrease in service utilization, leading to a lower number of antibiotic prescriptions for those on the co-payment plan, as compared to those on the full cover plan (Ahiabu et al., 2016).

The International Nonproprietary Name (INN) system was developed by the WHO in 1950, to provide health professionals with a unique and universal name to identify each pharmaceutical substance (WHO, 2017a). This is important for the clear identification, sale, prescription, and dispensing of medicine to patients, as well as for good communication and exchange of information among health professionals and scientists worldwide (WHO, 2017a). At medical institutions, strictly generic names are used for medicines during teaching; however, in practice, the prescribers prescribe by brand name, which might be influenced by external factors, such as the type of facility, role of the pharmaceutical representatives, patient load, and the financial incentives to prescribers, for prescribing certain brands (Ojo et al., 2014). According to the WHO (2001), generic medicine could be between 50% and 90% cheaper than their equivalent originator. The WHO recommended that medicines be prescribed in generic names as a safety measure for patients, since it provided universal information and simplified communication among healthcare providers (Atif et al., 2016). Generic substitution by pharmacists is allowed and encouraged, generally; however, generic substitution is not mandatory in some countries, including South Africa, as substitutions could be overridden by a prescriber, as well as the patients (Steinman, Chren, & Landefeld, 2007). In South Africa, pharmacists are bound by law to inform patients of the available generic version, and dispense generic medicine; unless the patient refuses it; it is forbidden by the prescriber, in writing; the generic medicine cost more than the originator; or is

declared unsuitable by the government (Republic of South Africa [RSA], National Department of Health [NDoH], 1997).. Therefore, the use of generic medicines should be encouraged, as it reduces cost, limits commercial influence, and reduces potential for prescribing errors, because the confusion of medicine names may result in ADR. It has been observed that prescribers refer to medication by their brand names, and this potentially unnecessary use of brand names for medication, may reflect the prescribers', and the patients' belief that generic formulations are inferior to brand medicines (Steinman et al., 2007).
South African government has establish a NDP to regulate and develop a pricing plan for medicines, ensure that medicines are tested and evaluated for effectiveness, develop EMLs and STGs to be used by the public, and plan for the increased use of generic medicines, as well as the effective procurement of essential medicines (Republic of South Africa [RSA], National Department of Health [NDoH], 1996). The South African NDP, section 7.5, advocates for the establishment of a Pharmacy and Therapeutic Committee (PTC), also referred to as DTC, in all hospitals (public and private), to ensure the rational, cost-effective supply and use of medicines (RSA, NDoH, 1996). The PTC could provide leadership and ensure that patients are provided with the best, cost-effective quality of care, by determining the medicines that will be available, the cost, as well as how they should be used (Holloway & Green, 2003).

A functional PTC at provincial, district, and facility level, is the cornerstone of the South African NDP (Systems for Improved Access to Pharmaceuticals and Services [SIAPS] Program, 2012). The PTC is expected to develop and implement a cost-effective formulary system, consistent with the national STG. In addition, it is expected to ensure that the available medicines are only of a high quality, efficacious, safe, and cost effective. The PTC is also expected to ensure that there is a system to monitor, detect, report, and prevent ADR, as well as frequently monitor and evaluate medicine use, to develop and implement interventions to improve RMU by prescribers, dispensers, and patients (MSH, 2012). The national PTC should encourage the establishment of PTCs at facility level, develop STGs for most prevalent diseases, provide national training for healthcare providers, strengthen regulatory systems, as well as provide RMU training for the general public (Green et al., 2009). The WHO's approach to establishing PTCs as the core intervention to promote RMU, has been adopted by the South African government. Effectively, the PTCs are expected to support healthcare organisations, by providing equitable access to safe, effective, cost-effective, and affordable medicine, as well as ensure quality care to all citizens in the country. Additionally, it must ensure the availability of essential medicines, to improve the quality of therapeutic care in the public, as well as the private sector (Republic of South Africa [RSA], National Department of

Health [NDOH], 2015). The PTC is a multi-disciplinary forum intervention to promote RMU; however, their impact on clinical, or economic improvement, has not really been evaluated in developing countries (Laing et al., 2001).

The availability of a formulary, or EML, would improve rational prescribing and dispensing practices, subsequently improving patient care (Otoom, Batieha, Hadidi, Hasan, & Al Saudi, 2002). Medicine selection should be closely linked to the WHO treatment guidelines, medicine inclusion decisions should be evidence-based, rather than by consensus, cost consideration should be separated from safety and efficacy evaluation, and the EML development process needs to be done continually, instead of in two-yearly updates (WHO, 2001). Access to non-formulary items should be provided in a structured format; however, it should be monitored to prevent misuse (Laing et al., 2001).

The dissemination of guidelines is an important factor, which contributes to the success of changing the practice, while other factors include the credibility of the group involved in the developing process, the complexity of the targeted practice, the involvement of end-users, and the resulting format of the guidelines. Additionally, if the guidelines were focused on improving the quality of care, instead of reducing costs, they would gain great acceptance (Laing et al., 2001). The implementation of local guidelines, as well as monitoring their use, improved documentation, standardisation of forms, and the timely education of prescribers, are cost-effective strategies that could be employed to improve the appropriate prescribing of antibiotics, even in poor resourced countries, or facilities (Lim et al., 2015). It is important to monitor antimicrobial use in countries, continuously, to explore factors that influence their inappropriate use, and enable the creation of relevant intervention, to retard the pace of resistance development (Ahiabu et al., 2016).

When microbiological testing identifies a causative organism, treatment must be changed to the narrowest agent that would treat that organism effectively (Boyles et al., 2017). Regardless of the high infectious disease burden rate in developing countries, not all antibiotic prescribing and use are appropriate, as, in a study conducted in Ghana, with 693 in-patients with fever, only 11.3% of the patients were inflicted with bacterial infection (Ahiabu et al., 2016). It is essential that the correct empirical antibiotic be administered, and to achieve this, surveillance data for the causative organism, as well as the resistance occurrence of antibiotics in the particular community, or population, must be collected regularly, as pre-exposure to antibiotics must be taken into consideration (Bosch, Van Vuuren, & Joubert, 2011). Brink et al. (2016) suggest a delay in antibiotic prescribing for throat infection, while awaiting the microbiology culture and sensitivity (MC&S) results, as the delay would not reduce the efficacy of rheumatic fever prophylaxis. While in the United Kingdom, the National Institute of Health and Clinical Excellence (NICE) guidelines do not recommend antibiotic prophylaxis for patients receiving dental, or non-dental procedures (Parrish & Maharay, 2012), which indicates the importance of taking into consideration local factors, such as the prevalence of HIV/AIDs and rheumatic heart disease, when adapting international guidelines.

In South Africa, antimicrobials are available by prescription only, prescribed by medical practitioners (including Dentistry), registered with Health Professional Council of South Africa (HPCSA); however, the legislation makes provision for nursing practitioners (Republic of South Africa [RSA], Nursing Act, Act No. 33 of 2005, section 56[6]), and pharmacists (through a Primary Care Drug Therapy [PCDT] licence), to diagnose and prescribe antibiotics, as well as other common illnesses limited to STG (Republic of South Africa [RSA], Pharmacy Act, Act No. 53 of 1974). To contain the spread of AMR, the cost-effective interventions should include the formation of a multi-disciplinary forum, which involves antimicrobial resistance surveillance, as well as promote rational use of antimicrobial and infection control (Brink et al., 2006). In hospitals where ASP has been implemented, success in reducing antimicrobial use has been observed, mitigating AMR, and improving patient outcomes (Chunnilall et al., 2015). ASP is a requirement for hospital accreditation in Canada (Hogan, Gazarin, & Lapenskie, 2016).

In South Africa, a Cape Town central hospital established a weekly multidisciplinary ward round, specifically for antimicrobial stewardship, which has revealed a decrease of 19.6% in antibiotics prescribing (without an increase in patient mortality), 30 days readmission rate, and a decrease of 35% in the budget of antibiotics (Mendelson, 2015). Kumar et al (2006) found that the administration of effective antimicrobial within an hour to patients with septic shock was associated with survival rate of 79.9% while every hour delay was associated with decrease in survival of 7.6%. Pharmacist-driven antimicrobial protocol for ensuring patients received intravenous antimicrobial within an hour from been prescribed, conducted in 33 private Netcare hospitals within South Africa has shown an improvement in adherence to hang-time protocol from 41.2% pre-intervention to 78.4% post-intervention (Messina et al, 2015). The ASP carried over four year period in Groote Schuur hospital, South Africa, has shown reduction in total antimicrobial usage particularly intravenous without adverse effects (Boyles et al, 2017). Pharmacist visit to intensive care units in Steve Biko Academic hospital, South Africa, has resulted in discontinuation of antimicrobial after completing the course, antimicrobial prophylaxis after 24 hours and pantoprazole continuous infusion for gastric bleeding after 72 hours (Bronkhorst et al, 2014). The existence of ASP in Groote Schuur hospital, in South Africa, has resulted in decreased 35% cost in antibiotic budget without a change in in-patient mortality and 30 days re-admission rate following weekly ward-rounds (Boyles et al, 2013).

The corner stone of ASP is the switch from the intravenous method to oral therapy, and the use of the minimum effective duration of therapy (Boyles et al., 2017). However, the most effective strategy to reduce AMR was strict infection control measures, to optimize both therapeutic and prophylactic antimicrobial use through active surveillance, as well as establish protocols, education, and stewardship (Ramsamy et al., 2013). The dearth of studies conducted in rural and district hospitals has been a barrier to the development and implementation of ASP (Hogan et al., 2016). Other constraints that restricted ASP, as well as good infection and prevention control (IPC) practices include, the unavailability of procurement data from Intercontinental Marketing Services (IMS), currently IMS health (data on antimicrobial consumption, only available in the private sector), and the lack of reliable evidence, which hampers ASP efforts and evaluation of stewardship interventions (Schellack et al., 2017).

Baseline antimicrobial utilization data could guide research initiatives that could provide a clear understanding of different measures of antimicrobial use, and the level of resistance; however, in low-resource settings it is still a challenge to determine antimicrobial consumption data (Schellack et al., 2017; Kotwani & Holloway, 2011; Truter, 2015). The use of antibiotics needs to be monitored in all countries. Simultaneously, the factors that promote irrational antibiotic prescribing and use need to be explored, while relevant interventions, to slow down the pace of resistance, need to be developed (Ahiabu et al., 2016).

The national strategic plan to combat AMR in South Africa has core standards for ASP, which will be monitored by the office of Health standards and compliance. These standards include the establishment and implementation of stewardship committees at district and facility levels (Mendelson, 2015). The South African National Department of Health (RSA, NDoH, 2014) states that its ASP aims to optimize antimicrobial use and reduce the emergence of AMR, without compromising patient care. In South Africa, the ASP guidelines for antibiotic prescribing in adults are available and aligned with the national EML and STG. It provides an algorithm approach to prescribing, as well as treatment duration, and is available as the *SAASP app* across platforms (Mendelson, 2015).

For strategies that combat AMR to achieve success, three pillars need to be considered, namely: firstly, improve the surveillance and reporting of AMR, to gain knowledge of the local resistance pattern (which will help in the selection of the correct antimicrobial); secondly, once the causative microbial is identified, use the correct antimicrobial, or empirical antibiotic, to optimize its use, and thirdly, ensure that infection control and prevention practices are in place, as well as improve access to and coverage with vaccines (Mendelson, 2015). The problem of irrational prescribing has been observed to be increasing in developing countries, despite the many intervention measures that have been implemented, including educational, managerial, financial, and multifaceted interventions (Bbosa et al., 2014). Medicine utilization needs to be studied, continuously, in facilities, or regions, to determine how medicines are misused, or overused, as well as whether poor access to up-to-date unbiased medicine information from healthcare providers, does influence irrational use. Subsequently, such studies need to be published to create awareness and improve the situation (Arora et al., 2017).

Problem-based educational intervention has been observed to be more effective, when it is repeated on multiple occasions, more focused on practical skills, and linked to the use of the STG (Laing et al., 2001). Healthcare workers must be introduced to sources of unbiased updated information, to ensure that they do not to depend, solely, on sale literature and the prescribing guides of pharmaceutical companies (Arora et al., 2017). The most accessible and established sources of medicine information are the pharmaceutical industries that aim is to promote certain products, rather than the improved quality of care (Laing et al., 2001). Prescribers must be trained to appraise the literature, and be able to critique promotional materials, as access to sound medicine information does not guarantee appropriate prescribing; however, it is a basic requirement for RMU decisions (Edrees & Elkhward, 2014).

Despite the high level of irrational use of medicine, through self-medication, little, or no community education on RMU has been observed (Akinyadenu & Akinyadenu, 2014). Even in this current age/era of information, individuals are still unable to educate themselves about medication, as patients might have heard of the word, *antibiotics*, but may not be aware that it should be used for infectious diseases only, and for a fixed period (Chandy, 2008). A strategy needs to be developed, and a community-based project needs to be implemented, to promote RMU at house-hold level (WHO, 2001). Prescribers and pharmacists need to spend more time with patients, educating them about their conditions and the appropriate use of medicine, as over time it could make a significant impact on community awareness (Otoom et al., 2002).

Public education is important if medicines are to be used more rationally, and household expenditure is to be reduced; therefore, training remains an important cost-effective intervention for the improvement of RMU (WHO, 2001). Public awareness of the negative consequences associated with inappropriate medicine use should be raised, and information disseminated on strategies to improve the practice of appropriate medicine use (Akinyadenu & Akinyadenu, 2014). As important as it is to educate the public about RMU, healthcare providers should also be encouraged to recommend, or prescribe medicine only when necessary, and to suggest appropriate home remedies (Arora et al., 2017). Advancing the balanced utilization of solutions requires powerful strategies, as well as cooperation between wellbeing experts, patients, and the community (Sabir, 2018). In Zambia, the findings of a study on continuing educational intervention revealed a decrease in the average number per prescription, from 2.3 to 1.9, and a reduction in antibiotic use (Laing et al., 2001).

Students, who had received training with the WHO guide to good prescribing, have been observed to prescribe more competently, than those who did not receive this training (Laing et al., 2001). South Africa, Japan and the Netherlands offer medical students and lecturers two weeks practical training with the WHO guide. In addition, this manual is currently adapted for pharmacists' and nurses' training in Ghana and South Africa, respectively (Laing et al., 2001).

Elderly patients are most likely to be diagnosed with more than one condition, and probably interact with various prescribers, as the largest population to receive polypharmacy; therefore, it is important to maintain ample knowledge about prescribing for adults (Spinewine et al., 2005). There are several criteria and tools that could be used to improve rational prescribing to the elderly, such as the Beers criteria list, to assess potential inappropriate prescribing (Van Heerden, Burger, & Gerber, 2016). According to Steyn et al. (2008), public clinics that mostly treat acute conditions, manage chronic diseases inadequately, or unsuccessfully attempt to assess risk factors, and exercise a patient-centred healthcare approach, which leads to the poor adherence of patients. A study conducted in USA, Australia and South Africa, determined that 40%, 20%, and 30% of patients >60-years-of-age, respectively, received at least one inappropriately prescribed medicine (Van Heerden et al., 2016).

2.5. Describe the role of pharmacist/pharmacist student in improving RMU

Pharmacists are in a strong position to promote RMU, because of their extensive knowledge of medicine and communication (Arora et al., 2017). In addition, pharmacists are well placed to advise on the management of health conditions, participate in health education and promotion, contribute to the safe, appropriate use of medicine, and provide patients with adequate medicine information, as the principle of RMU (Prokic et al., 2014). The pharmacist is often the last person to see the patients before they leave the hospital; therefore, the pharmacist has an immense responsibility to advise patients (Amin et al., 2011). The WHO recommends a special role for pharmacists, namely, quality assurance, as well as the safe and effective administration of medicine (Arora et al., 2017). Gasson et al. (2018) recommend empowering pharmacists as gatekeepers to ensure the appropriate use of medicine and correct prescribing.

The pharmacist's central activities of dispensing are giving advice and providing safe medicine (Smith, 2004). Dispensing is regarded as an important component to promote more rational use of medicine; however, research on good dispensing practice is scant (Arshad et al., 2016). The pharmaceutical care role of pharmacists is still not acknowledged by some pharmacists, and there is no clear social commitment, defined by the pharmacy profession, which reflects the clinical intervention of a pharmacist (Hepler & Strand, 1990). Pharmacists, as the primary dispensers, are responsible to re-enforce the patient's knowledge of their medicine, and educate, or advise other healthcare providers on the appropriate use of medicines (Abdulah et al., 2014). The patient's adequate knowledge of medicines is very important to prevent the misuse and overuse of medicines (Latif et al., 2013).

The patient's adherence is likely to improve, when they understand the benefits of taking their medications as instructed, and appreciate the risk of non-adherence; therefore, the engagement of a dispenser and a patient has a significant effect on medicine use of the patient (Ofori-Asenso & Agyeman, 2016). Consumers view the pharmacist as the sole expert of medicine, rather than of health and illness (Eades, Ferguson, & O'Carroll, 2011). A study conducted in Indonesia determined that many patients do not understand the role of pharmacists to their healthcare, and assume pharmacists only dispense medicine (Abdulah et al., 2014). Pharmacists are expected to provide quality pharmaceutical service, which depends on their training, knowledge, communication skills, and time spent with the patient, an optimal dispensing period being 60 seconds (Prokic et al., 2014). The shorter the time that the pharmacist spends with the patient, while dispensing, the less information is provided to the patients, regarding their medicine regimen, ADRs, and precautions, resulting in non-compliance, poor outcomes, and adverse events (Latif et al., 2013).

The pharmacist's role as a healthcare professional, is not perceived as important by the community or other healthcare professions; consequently, they are still underutilised in developing countries (Arora et al., 2017). The pharmacist has the potential to contribute in primary healthcare (PHC), by providing advice in self-care or self-medication, especially in combating medicine abuse, and promoting RMU. However, some studies have revealed that pharmacists display little interest in patients' health, and are more profit-oriented, resulting in inappropriate sales of antibiotics. Consequently, patients view them as retailers and business people, instead of healthcare providers (Akinyadenu & Akinyadenu, 2014). In South Africa, pharmacists may sell more, or less than the quantity of antibiotics prescribed; however the quantity may not be more than +/– 5% of the quantity prescribed (Republic of South Africa [RSA], National Department of Health [NDOH], 1997).

Pharmaceutical services need to restore what has been missing for years; "a clear emphasis on the patient's welfare, a patient advocacy role with clear ethical mandate to protect the patient from harmful effect", and accept the social responsibility to reduce and prevent medicine-related morbidity and mortality (Hepler & Strand, 1990, p. 534). Pharmaceutical services such as pharmacokinetic dosing, therapeutic monitoring, and medicine information, may extend the functions, legitimate competence, and boost the professional status of pharmacists; however, if they do not display professional responsibility for patient welfare, they cannot fulfil a professional role (Hepler & Strand, 1990). In addition to the pharmacist's community role of educating patients on the correct use of medicines, they are expected to assume a leadership role in promoting RMU, in both health care and the community environment. In the hospital setting it is legally binding that pharmacists actively participate in hospital PTC that monitor medicine use (RSA, NDOH, 1996), and adopt stewardship for the rational use of antibiotics.

The South Africa Pharmacy Council (SAPC) serves to guide pharmacists and hold them accountable, as its standards emphasize a practice philosophy, patient respect, and the pharmacist's role within a multidisciplinary team (South African Pharmacy Council [SAPC], 2010). Several studies reflect the impact of the pharmacist's intervention in promoting RMU. One such study reported the irrational use of prophylactic acid suppressants for patients undergoing elective hepatobiliary operations. The pharmacist actively intervened, by checking whether prophylactic acid suppressants were indicated or not, prior to the procedure, which intervention initiated a significant reduction in the use of prophylaxis that were not indicated, or the inappropriate medicine choice, dose, route, as well as unnecessary replacements, and prolonged duration of the prophylaxis (Luo, Fan, Xiao, & Chen, 2017). Proton-pump inhibitors (PPIs) were also observed to be over-prescribed, and with the pharmacist's intervention, the overutilization of PPIs has been reduced, along with its associated costs (Bundeff & Zaiken, 2013). The improvement of a number of patients with rational indicators was identified, after the correct route of administration. Consequently, the duration of therapy was decreased, and the mean total cost of PPIs and hospitalization were reduced (Xin, Dong, Lin, & Li, 2018).

The rational use of antibiotics requires special attention, since the increased spread of resistance has become a worldwide threat (Truter, 2015; Junaid, Jenkins, Swanepoel, North, & Gould, 2018; Brink et al., 2016; Hashemi et al., 2013). The findings of a study conducted by Zhou, Ma, Gao, Chen, and Bao (2016) revealed that the intervention of pharmacists initiated significant improvement in the rational antibiotic prophylaxis, antibiotic selection, correct timing of the first dose of prophylaxis, appropriate duration of prophylaxis, as well as a decrease in unnecessary antibiotic replacements and combinations. In addition, it resulted in favourable outcomes, which included a decrease in antibiotic prophylactic costs, hospitalization days, as well as a decline in the rate of antibiotic resistant Klebsiella pneumonia, and *Staphylococcus aureus* cases.

2.6. Review current literature for educational outcomes related to medicine utilization evaluation

Chronic patients, namely those with diabetic and hypertension challenges, usually require multiple medications that could contribute to non-adherence by patients, and consequently, morbidity and mortality, which is a financial burden to the health service. Therefore, it is important to assess the medicine use of chronic patients, regularly (Eze Uchenna & Odunayo Oluwakeni, 2010). A study, in which 2500 patients were interviewed, one third had marginal, or inadequate health literacy, of which 42% misunderstood the directions about taking medications on an empty stomach, 25% misunderstood their return dates, and close to 60% were unable to read (Martin et al., 2005). The patients' beliefs are affected by health literacy, and in practice, the patient's low health literacy is linked to ineffective provider-patient communication (Martin et al., 2005). It is common that elderly individuals would be more forgetful than younger ones, as according to Martin et al. (2005), patients forget 56% of their instructions shortly before leaving the hospital.

In another study, conducted at a private hospital in Kwazulu-Natal, the findings revealed that 61.0% of the patients in the intensive care unit (ICU) received antibiotics. For 41.1% of these patients, the antibiotics was not indicated, 29.8% had an inaccurate choice of medicine, and 8.9%

had incorrect dosing (Chunnilall et al, 2015). Schellack et al. (2017) collected data for 3 years, and observed a 20% reduction of middle/narrow spectrum penicillin in the private sector, while broad spectrum penicillin remained at the market share level of 35%, declining at a rate of 2%. Simultaneously, they observed a 16% increase of daptomycin, fusidic acid, linezolid and tigecycline. However, in the public sector, they observed an increase in injectable quinolones, injectable cephalosporin, and broad spectrum oral penicillin, which might be due to the unfamiliarity with appropriate antimicrobial prescribing practices, the inappropriate use of first line therapies, the desire to use newer, more expensive therapies, as well as the possible increase in resistance.

According to Santos and Nitrini (2004), speciality clinics or wards are more likely to prescribe antibiotics, as opposed to general wards. The findings of their study in South East Brazil revealed that 28.9% antibiotics prescriptions originated from paediatricians, and 13.7% from clinicians (Santos & Nitrini, 2004). The findings of a study conducted by Gupta et al. (2011) revealed a wide variation of antibiotic prescribing practices, despite published evidence-based guidelines for the optimal selection of antimicrobial agents, as well as the duration of treatment. Acute uncomplicated cystitis, lower respiratory infection [LRTI], healthcare associated infection [HCAI], and surgical procedures, are some of the common indications for antimicrobials prescribing (Brink et al., 2066, 2006; Gupta et al., 2011; Napolitano et al, 2013). The findings of a study conducted in Iran on outpatients receiving antibiotics revealed that the most common diagnoses were upper respiratory tract infection, as common colds (29.2%), and sore throats (11.8%), while the most common route of administration (22%), was the parenteral route (Hashemi et al., 2013). Regarding acute uncomplicated cystitis, the current guidelines suggest that fluroquinolones are highly efficacious in a shorter duration of a 3 day regimen (Gupta et al., 2011); however, in practice, a longer duration of 5-7 days is prescribed. Amoxicillin or ampicillin should not be prescribed as an empirical treatment, world-wide, due to its relatively poor efficacy, and high prevalence of AMR (Gupta et al., 2011).

Approximately 30% of patients, undergoing surgical procedures, will develop post-operative surgical site infections [SSI], which result in the readmission of the patient, and consequently, increased healthcare costs (Lim et al., 2015). The optimal time for the administration of preoperative doses, is within 60 minutes before any surgical incision. For the antimicrobial agent to prevent SSI, the appropriate dose must be administered at a time that will ensure adequate serum and tissue concentration, referred to as the minimum inhibition concentration [MIC], for the period of the procedure (Bratzler et al., 2013). According to the South African Society of Anaesthesiologists (SASA, 2014), the MIC of the antibiotic of choice must be achieved for the period of incision to wound closing. A single dose is generally indicated in the prophylaxis, except in cases such as a large bowel intervention, and the insertion of a prostheses, where contamination is a risk (Bonello & Stafrace, 2016). The shortest effective dose is unknown; however, researchers aver that post-operation doses are not necessary for most procedures (Bratzler et al., 2013), and the duration of prophylaxis should not exceed 24 hours after the surgery (Bonello & Stafrace, 2016), as prolonged antibiotic prophylaxis, after a procedure, has indicated no extra benefit (SASA, 2014).

Other literature reviewed that used the WHO/INRUD drug use indicator as a prescribing indicator, to evaluate good prescribing practice, are listed in the Table 2.1 below, which indicates that polypharmacy is practiced across the world, the excessive use of antimicrobial agents varies from one country to another, as with injections, and the prescribing of medicine, by generic name, is still a worldwide challenge.

Table 2.1: Reviewed articles for prescribing indicators across the world

Country	Health care sector	Average medicine prescribed	Percentage generic	Antimicrobial	Injections	From EML	Study reference
Tertiary Paediatric Hospital in Sierra Leone	Tertiary Paediatric Hospital (Public)	3.77	71.0%	74.8%	21.1%	70.6%	Cole et al., 2015
Ribeirão Preto, South Eastern Brazil	Regional referring centre (Public)	2.2	30.6%	21.3%	8.3%	83.4%	Santos et al., 2004
10 provinces in Western China	Primary healthcare (PHC) (Public)	2.36	64.12%	48.43%	22.93%	67.70%	Dong et al., 2011
Community pharmacies in Southern India	Community pharmacies (Private)	3.7	2.5%	22%	7%	99.8%	Aravamuthan et al., 2017
Eastern Nepal	Community pharmacies (Private)	2.14	45.18%	40.44%	3.44%	76.11%	Chapagain et al., 2016
Ghana	PHC (Public)	4.01	79.2%	59.9%	24.2%	88.1%	Ahiabu et al., 2016
Tanzania	Public and Private	2.3	95.7%	67.7%	18.1%	96.7%	Irunde et al., 2017

	healthcare facilities						
Pakistan	PHC (Public)	3.4	71.6%	48.9%	27.1%	93.4%	Atif et al., 2016
Ethiopia	Academic and referral hospital (Public)	1.9	98.7%	58.1%	38.1%	96.6%	Dasalegn, 2013
Alexandria, Egypt	PHC (Public)	2.5	95.4%	39.2%	9.9%	95.4%	Akl et al., 2014
South Africa baseline (1996-1998)	PHC (Public)	2.5	36%	36%	11%	65%	Peltzer et al., 2006
South Africa Survey (2003)	PHC (Public)	2.2	37%	37%	5%	90%	Peltzer et al., 2006
South Africa, WC (2005)	PHC (Public)	3.0	48.7%	53.2%	6.4%	91.9%	Peltzer et al., 2006
South Africa, LP (2005)	PHC (Public)	3.4	41.7%	56.7%	9.7%	90.3%	Peltzer et al., 2006

CHAPTER THREE

RESEARCH METHODOLOGY

3.1. Empirical investigation

The empirical investigation was cross-sectional, which is observational by nature and well known as descriptive research, implying that it could not be used to determine the cause of a phenomenon, for example a disease (Cherry, 2019). This current study involved collecting retrospective data from existing medical data records to establish whether medicine was being used rationally at public health care facilities in the Limpopo Province. The steps followed during the empirical investigation are discussed in the subsequent sections.

3.2. Study setting and population

The study was conducted at various health care facilities, including district and regional level hospitals, in the Limpopo Province, South Africa (see Table 2.1). The district hospitals serve a defined population within their districts, they support primary healthcare (PHC), and they provide services that includes in-patient, ambulatory health services and emergency health services. District hospitals get support from general specialist based in regional hospitals, and number of beds of 50 to 600 depending on size of hospital. The health services in regional hospital include internal medicine, paediatrics, obstetrics and gynaecology, and general surgery, they get support from tertiary hospitals. The regional hospitals have 200 to 800 beds, number of beds per selected hospital in study see Table 2.1. In South Africa, the public healthcare sector is estimated to cater for the majority of the population (84%), while the private sector only caters for 16% (Schellack et al., 2017). For prescribing and antimicrobial use indicators, the existing medical data records of all patients (children and adults), who had received pharmaceutical services at the health facilities, were included in the study, implying in-patient as well as out-patient visits. Therefore, all patients who did not receive pharmaceutical services were not included in this study, for example, all those patients, who only received non-pharmacological therapy, such as a visit to the psychologist. In addition, the facilities that agreed to participate, also agreed to the pharmacists in charge of their pharmacies to complete structured questionnaires for facility indicators.

3.3. Study design

The design belongs to the category of the quantitative, non-experimental design methods, since the researcher will not attempt to influence the patients (participants), or their surroundings, through manipulation or intervention. Observational studies are conducted, when the investigator observes the natural relationship between factors, as well as the outcomes, and does not act upon the study participants' information (Thiese, 2014). The study design was deemed suitable for this current study, since data would be collected from aggregate data sources, such as patient medical records.

Additionally, this current study was a descriptive retrospective one, since data was collected from past events, specifically, existing medical data records. Descriptive research studies examine the situation in its current state, and are limited to the description of the occurrence, which may be prevalence/incidence (Joubert & Ehrlich, 2012). According to Thiese (2014), retrospective designs measure variables from past events.

A quantitative research approach focuses on logical concepts within the research, as well as on measurable aspects of human behaviour (Brink, 2012). The research could be used in response to questions of variables in the research, and involves the collection of data (Williams, 2011). In addition, the study design has a quantitative approach, as variables will be measurable in the study. The methodology for this current study was adopted from the World Health Organization (WHO, 1993) documents on rational medicine use, "*How to investigate drug use in health facilities*", and the Systems for Improved Access to Pharmaceuticals and Services [SIAPS] Program, "*How to investigate antimicrobial use in hospitals: selected indicators*" (SIAPS, 2012).

3.4. Sampling

Sampling was done in two stages. In the first stage, the health facilities, including both regional and district hospitals, were selected, based on their willingness to participate in the study, which included the pharmacists/PTC secretaries in charge of the pharmacies, for the structured interviews. In the second stage, patient folders were selected through convenience sampling, without seeing the patients collecting medication from the pharmacies, at the selected health facilities. Sampling was highly dependent on the availability of human resources at the health facilities, willingness to participate, as well as the type of service provided at the health facilities.

The World Health Organization (WHO, 1993) recommends that at least 600 encounters be included in a cross-sectional study; therefore, 20 health facilities, to represent the large group of health facilities, and at least 30 patient encounters from each facility, were recommended for this type of study (30 patients in each of 20 facilities = 600 patients). In the event that more than 30 patient encounters were possible, it would be encouraged. Limpopo Province comprises five districts; therefore, four facilities were selected in each district. Selection was made through convenience sampling, and ensured that the facilities were easily accessible to the researcher, in a limited time. In Table 3.1, the researcher presents the number of hospitals per district, and indicates the units selected.

Table 3.1: Complete list of hospitals in Limpopo Province.

District Name (number of hospitals)	Name of hospitals	Recruited hospitals	Number of beds
Capricorn district (9)	1. Botlokwa hospital	X	56
	2. Helen Frans hospital	X	149
	3. Lebowakgomo hospital	X	252
	4. Mankweng Hospital		
	5. Polokwane hospital		
	6. Seshego hospital		
	7. Thabamoopo hospital		
	8. W.F Knobel hospital		
	9. Zebediela hospital	X	108
Mopani district (6)	10. Kgapane hospital	X	262
	11. Letaba hospital		
	12. Maphutha L. Malatjie hospital	X	100
	13. Nkhensani hospital	X	360
	14. Sekororo hospital	X	208
	15. Van Velden hospital		
Sekhukhune district (7)	16. Dilokong hospital	X	324
	17. Groblersdal hospital		
	18. Jane Furse hospital		
	19. Matlala hospital	X	120
	20. Mecklenburg hospital	X	105
	21. Philadelphia hospital		
	22. ST Ritas hospital	X	400
Vhembe district (9)	23. Donald Fraser hospital		
	24. Elim Hospital	X	550

	25. Evuxakeni hospital		
	26. Hayani hospital		
	27. Louis Trichardt hospital		
	28. Malamulele hospital	**X**	**256**
	29. Messina hospital		
	30. Siloam hospital	**X**	**350**
	31. Tshilidzini hospital	**X**	**538**
Waterberg district (8)	32. Ellisras hospital	**X**	**130**
	33. F.H Odendaal hospital		
	34. George Masebe hospital	**X**	**260**
	35. Mokopane hospital	**X**	**273**
	36. Thambazimbi hospital		
	37. Voortrekker hospital	**X**	**91**
	38. Warmbaths hospital		
	39. Witpoort hospital		
Regional hospitals (6)	Letaba hospital		
	Mokopane hospital	X	**273**
	Philadelphia hospital		
	ST Ritas hospital	X	**400**
	Tshilidzini hospital	X	**538**
	Warmbaths hospital		
Tertiary hospitals (2)	Mankweng hospital		
	Polokwane hospital		
Special hospitals (3)	Evuxakeni hospital		
	Hayani hospital		
	Thabamoopo hospital		

3.5. Data-collection

In this current study, the data were collected from the patients' medical folders, as well as through interviews with the institutions' pharmacists in charge, on the day of data collection. The pharmacists were in charge of the facilities' pharmacies, and also acted as the institutions' therapeutic committee secretaries (RSA, NDOH, 1996). A retrospective study was employed to obtain the prescribing and antimicrobial indicators. For the prescribing indicators, the patient's medical folders were conveniently collected from the institutions' pharmacy, after medicines were dispensed, to ensure that hospital services were not interrupted. For the facility indicators, a structured questionnaire was used in interviews with the pharmacists in charge, to understand if unavailability of multi-disciplinary forum and reference resource might influence medicine use problem. These questionnaire ensued after comprehensive details of the study were explained to the pharmacists, on the day of data collection, and they had confirmed their understanding and consent, by signing a consent form. For the antimicrobial indicators, the patients' medical folders were collected from the wards, after the patients were discharged, and before the files were returned to the records department for filing. The WHO/INRUD core drug use indicator data were collected from October 2018 to December 2018, while the antimicrobial use indicator data were collected from October 2018 to March 2019, implying that the facilities were visited twice.

3.6. Data-collection tools

Standardized WHO tools for the investigation of medicine use in health facilities were utilized in this current study. These tools were adapted to suit the local context, or questions to be answered.

- ***Prescribing Indicator Tool*** *(Annexure A)*

  The researcher used this tool with the outpatient folders, after the patients had collected their medication, and focused on five key areas, related to the appropriate use of medicine. It evaluated the average number of medicines per encounter, medicines prescribed in their generic names, antibiotics prescribed, injections, and whether the medicines prescribed were on EML or formulary. This indicator provided information concerning medicine use, prescribing habits, tendencies of prescribing injections and antibiotics. For injection, vaccines, monthly antipsychotic injectable and insulin were not counted as injections. Antibacterial, dermatological and ophthalmological antibacterial agents were counted as antibiotics.

- ***Facility Indicator Tool*** *(Annexure B)*

  The researcher used this tool with the pharmacists in charge, or the PTC secretaries, in the interviews to determine the existence of the PTC, availability of the EML, STG for infectious diseases, and protocols for the prevention of infections. The researcher assumed that information they provided was completely correct.

- ***Antimicrobial Indicator Tool*** *(Annexure C)*

  This current study only focused in prescribing indicators for rational antimicrobial use. Inpatient folders of patients, who had received antimicrobials, while admitted, were used. Each case was assessed to ascertain whether the sensitivity test was conducted, the duration of the hospital stay and treatment, and how many antimicrobials were prescribed per patient (where one antimicrobial was prescribed in two different forms, for example, via intravenous and oral, it was considered one item). According to South African Statistics (StatsSA, 2003), influenza and pneumonia (5.2%) were ranked the second cause of death, following tuberculosis [TB]; therefore, in order to assess the quality of patient care, the management of pneumonia cases were evaluated, to ascertain whether the patients were managed according to STG.

3.7. Validity and reliability of data

Data was collected from patient medical records, using standardized tools, which had been adapted from validated WHO tools.

3.8. Data-collection process

The data were collected retrospectively, using WHO/INRUD standardized forms and the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program (2012). For the prescribing indicators, 30 files of out-patients, who had consulted the doctor on the day of data collection, were randomly selected and collected from the pharmacy, in the afternoon at each facility, after the patients had collected their medications. It included all out-patients with prescribed medicines except patients with human immunodeficiency virus (HIV) and/or tuberculosis (TB).

Additionally, on the day of data collection, after consenting to participate, the pharmacy managers/pharmacists in charge were given a questionnaire to determine the functionality of the facilities' Pharmacy and Therapeutic Committee (PTC), as well as the availability of infection control guidelines and protocols, namely, the Standard Treatment Guideline (STG), Essential Medicine List (EML), and Formulary, for facility indicators.

Each facility was visited twice, to access the rational use of antimicrobials. Ten inpatients' files from medical wards at each facility, were selected to test for the rational use of antimicrobials. The data were only collected from patients, who had been prescribed with antimicrobials during their hospital stay, after they were discharged, to determine their length of stay in hospital, as well as the duration of antimicrobials prescribed. It included all patients in medical ward who have received antibiotics during their hospital stay,

3.9. Data analysis

The researcher used the IBM Statistical Package for Social Sciences (SPSS) for Windows, version 25.0, to analyse the data statically, in order to obtain the standard deviations. To determine the degree of rational prescribing, the researcher adopted a previously validated method, utilized by Dong et al. (2011), to calculate the index of rational drug prescribing (IRDP). The IRDP comprises five categories of the WHO prescribing indicators. Each indicator is assigned an optimal index of 1; therefore, the closer the index is calculated to 1, the more rational the prescription. If the indicator index is calculated to be greater than 1, an index of 1 is assigned. The data are presented in table format.

The index of polypharmacy, rational antimicrobial, and injection indicators, were calculated using the formula below, which was also used by Atif et al. (2016). For the calculation of the index of non-polypharmacy, the optimal value of 1.8 was used. The generic name and EML indices were determined by the percentage of medicines prescribed by their generic name, and from the EML, respectively. The IRDP has the maximum optimal value of 5; therefore, it was determined by adding all the indices.

$$Index = \frac{\text{optimal value}}{\text{observed value}}$$

Regarding their ability to provide quality health care services, if any or all of following, namely, the latest edition of STG/EML hardcopy (adult hospital – 2015, and paediatric hospital – 2013), the adoption of the Limpopo Provincial Formulary, a developed facility formulary, as well as the utilization of the mobile app EML clinical guidelines, were existent at a facility, it was considered capable of providing quality health care. The primary health care STG/EML, regardless of the revision year, was regarded as inappropriate, since the study only included hospitals. For the facility indicators, the Index of Rational Facility Specific Drug Use (IRFSDU) was determined by the existence percentages of PTC, hospital formulary/EML, STG for infectious diseases, protocol for surgical prophylaxis with antimicrobials, and infection control guidelines. All five categories were assigned an optimal index of 1, and the total IRFSDU was determined by adding all indices together (See Table 3.2. below).

Table 3.2: Optimal levels of WHO/INRUD drug use indicators

Indicators	Optimal level	Optimal index
Prescribing Indicators		
% Prescriptions including antibiotic	<30	1
Polypharmacy prescription	1.6 – 1.8	1
% Prescriptions including injection	<10	1
% Medicine prescribed by generic name	100	1
% Medicine prescribed from EML or formulary	100	1
Facility indicators		
% Pharmacy and Therapeutic Committee	100	1
% Hospital formulary/EML	100	1
% STG for infectious diseases	100	1
% Protocol for surgical prophylaxis with antimicrobials	100	1
% Infection control guidelines	100	1

3.10. Statistical analysis

The data of this current study were analysed by using the programme IBM SPSS Statistics for Windows, version 25, while Microsoft® Office Excel version 15.0 was used to assist with the general calculations. Descriptive statistics were used to describe and summarise the data. It is customary to define a study population in descriptive studies, and subsequently, make observations on a sample selected from it (Banerjee & Chaudhury, 2010, p. 61). Descriptive statistics are used to organise, summarise, and display the data collected in a study (Hightower & Scott, 2012). *Frequency* is used to assist in describing the characteristics of the study populations. *Frequency* is the number of times an incident/phenomenon occurs, and is usually expressed as a percentage of the sample size (Maree, 2014). The occurence is usually measured in a unit of time.

3.11. Ethical considerations

3.11.1. Permission

The permission to conduct this current research was granted by the University of Western Cape Research Ethic Committee (Annexure D, ref: BM18/4/5) and Limpopo Province

Department of Health (Annexure E, ref: LP_2018_06_008). The researcher had no conflict of interest in the study.

3.11.2. Informed consent

Informed consent was received from all the participants, including the pharmacy managers, or delegated person(s), who were interviewed or questioned (Annexure F). Informed consent was necessary during the collection of the following information:

- Informed consent was required from pharmacy managers, or delegated persons(s), during the collection of information about facility indicators (Annexure F).
- All other activities utilized retrospective data obtained from the patients' folders; therefore, no consent was required. Approval to access patient folders was granted by the Department of Health, Limpopo Province.

3.11.3. Anonymity

In the data analysis phase, the researcher did not disclose the identity, or identify any specific individual, patient, or prescriber details, and ensured that no information could be traced back to any particular healthcare facility.

3.11.4. Confidentiality

The confidentiality of the patients and pharmacists was assured during the data collection and analysis processes, as all the collected data would be kept confidential. The researcher ensured that it would be impossible to link any data to a patient's identity, as the data were completely unidentifiable at the data analysis stage. However, the data collection forms will be kept in a locked location at the School of Pharmacy, University of the Western Cape, and data stored electronically in a password protected location.

3.11.5. Anticipated risks and precautions

There were no risks encountered during this current study, and it is the researcher's anticipation that the findings of the study will contribute to improved quality of care, for the benefit of all future patients.

3.12. Funding

There was no funding source for this current study.

CHAPTER FOUR

RESULTS

4.1. Introduction

In this chapter, the researcher presents the results, based on the research question of this current study. The World Health Organization and International Network for Rational Use of Drugs (WHO/INRUD) core drug use indicators and antimicrobial use indicators were used to evaluate the current medicine usage at 20 public healthcare facilities in Limpopo Province, South Africa. Four facilities per district (five districts) were recruited to participate in this current study, including district, as well as regional hospitals (Table 3.1). The researcher, firstly, provides a breakdown of the patients' demographic data in Table 4.1, and subsequently, the results are presented in three sections, namely, prescribing indicators, facility indicators, and antimicrobial use indicators.

4.2. Patient Demographic Data

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The ages of the included patients, ranged from 1 to 103 years, with a mean of 43.85, a standard deviation *(SD)* of 24.42, and an interquartile range (IQR) of 46.00 (25.00 – 63.00). The age distribution had a skewness of -0.08, a standard error (SE) of 0.10, and the kurtosis = -0.91 (SE = 0.20). The age distribution for females ranged from 1 to 99 years, with a skewness of -0.45 (SE = 0.13), kurtosis of 0.85 (SE= 0.26), median of 46 and IQR of 37. The age distribution for males ranged from 1 to 103 years, with a median of 45, IQR of 40, skewness of -0.12 (SE = 0.15), and a kurtosis of -0.98 (SE = 0.30). Ultimately, this study comprised 56.5% female patients (339) and 43.5% male patients (261), as illustrated in Table 4.1.

Table 4.1: Patient Demographic data

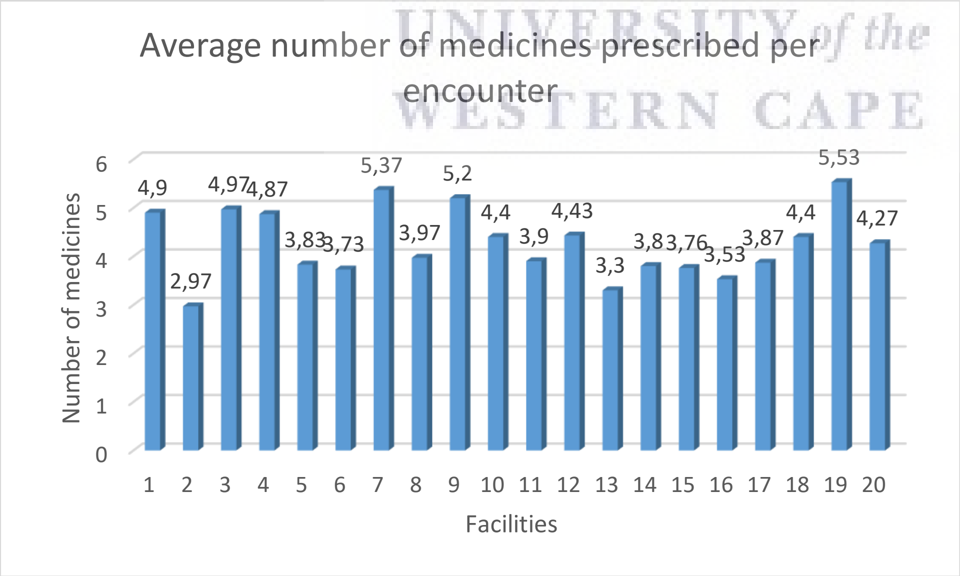
Facility Number	Average Age (Years)	Minimum age (Years)	Maximum age (Years)	Gender	
				Male (%)	Female (%)
1	48.73	3	95	9(30.00)	21(70.00)
2	42.07	3	89	14(46.67)	16(53.33)
3	45.40	5	88	13(43.33)	17(56.67)
4	49.20	1	86	13(43.33)	17(56.67)
5	42.97	1	88	15(50.00)	15(50.00)
6	35.37	1	79	14(46.67)	16(53.33)
7	47.40	4	96	9(30.00)	21(70.00)
8	52.97	1	98	12(40.00)	18(60.00)
9	49.10	21	79	13(43.33)	17(56.67)
10	50.23	3	86	15(50.00)	15(50.00)
11	43.97	1	103	16(53.33)	14(46.67)
12	48.93	9	79	19(63.33)	11(36.67)
13	37.13	1	99	18(60.00)	12(40.00)
14	36.60	4	85	6(20.00)	24(80.00)
15	49.13	2	99	14(46.67)	16(53.33)
16	38.00	1	84	9(30.00)	21(70.00)
17	37.07	3	51	14(46.67)	16(53.33)
18	48.47	1	86	14(46.67)	16(53.33)
19	42.3.0	1	90	9(30.00)	21(70.00)
20	32.00	1	69	15(50.00)	15(50.00)
Total	**43.85**	**1**	**103**	**261(43.5%)**	**339(56.5%)**
Age standard deviation		**24.42**			

4.3. Prescribing indicators

Data collection occurred between October 2018 and December 2018. A total of 600 patient folders were reviewed for the evaluation of prescribing indicators across 20 selected health facilities (see a map showing selected hospital distribution in Annexure H). The data were analysed, using IBM® Statistical Package for Social Sciences (SPSS) for Windows, version 25.0, to obtain the minimum, maximum, and standard deviation statistics. The degree of rational prescription was determined by calculating the index of rational drug prescribing (IRDP), which consisted of five indices, while a total IRDP was obtained by adding all the indices together.

The total of 30 out-patients encountered in each of the 20 facilities were included for evaluation in this current study. This resulted in a total of 600 prescriptions included for evaluation, in five domains of prescribing indicators, namely: *average number of medicines prescribed* (fixed dose medicines such as amoxicillin-clavulanate were counted as one medicine); *percentage of antimicrobials prescribed; percentage of injections prescribed*; *percentage of medicines prescribed under generic name;* and *percentage of medicines prescribed from the EML,* per encounter, while the IRDP was calculated to determine the degree of rational prescribing. Of the 600 patients included, the minimum medicine prescribed, per encounter, was 1, with a maximum of 17 (Table 4.3), a mean of 4.25, and a standard deviation (SD) of 2.54 (Table 4.2). It had a median of 4.00 (2.00 – 6.00), with a skewness of 1.20 (SE = 0.100), and a kurtosis of 1.68 (SE = 0.20), as per the frequencies of number of medicines prescribed per encounter in Table 4.3. According to WHO/INRUD, the optimal value of medicines prescribed per encounter is between 1.6 - 1.8; however, in this current study, 26.90% of patients received 2 or less items, 37.30% received 3 to 4 items, and 35.8% received 5 or more items (Table 4.3 and figure 4.1).

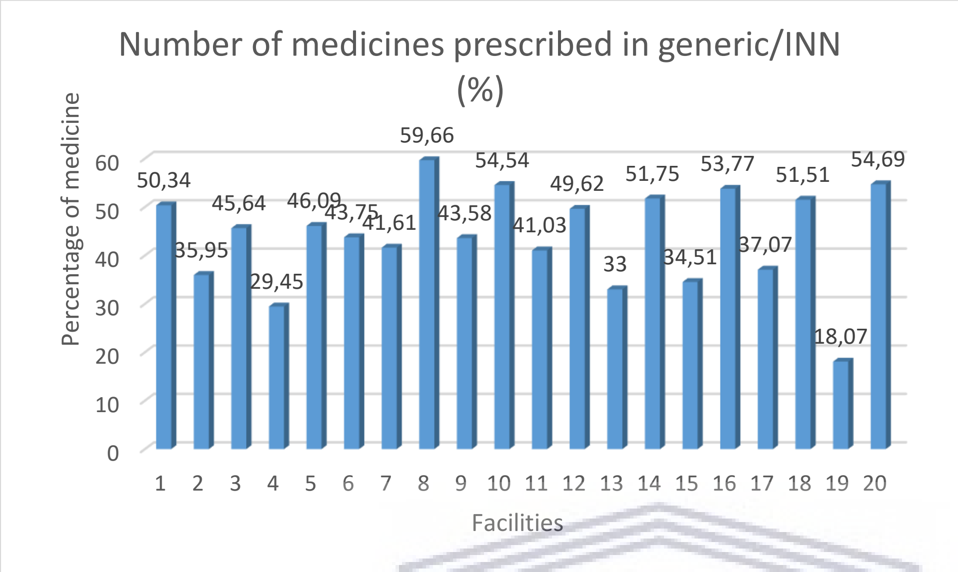
Figure 4.1: Average number of medicines prescribed per encounter



Of all the medicines prescribed, the minimum percentage that was prescribed, using the generic name, was 18.07%, with a maximum of 59.66%, and the average 43.78% (*SD* = 9.96). More than

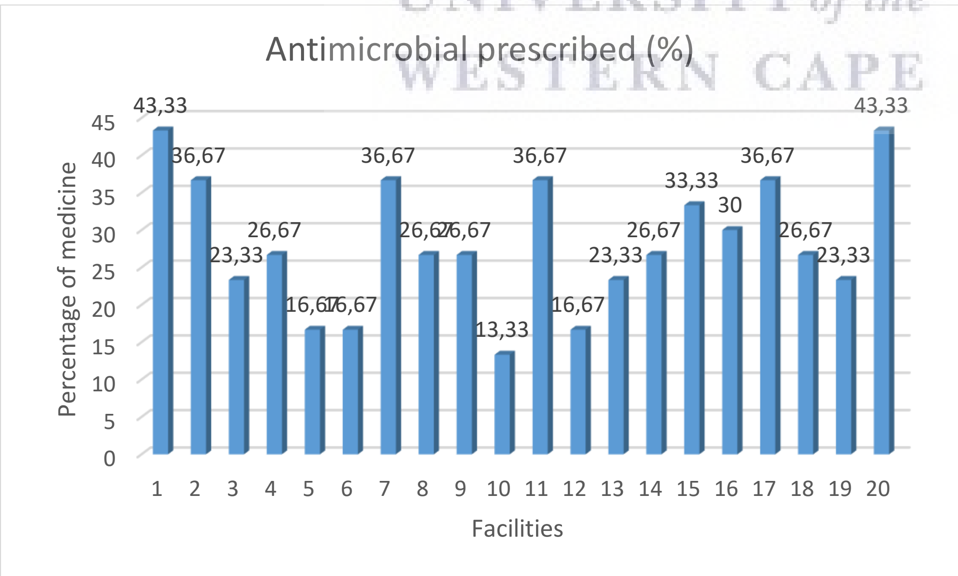
50% of medicines prescribed in all facilities were not prescribed by their generic names (Table 4.2 and figure 4.2).

Figure 4.2: Percentage of medicine prescribed in generic/INN



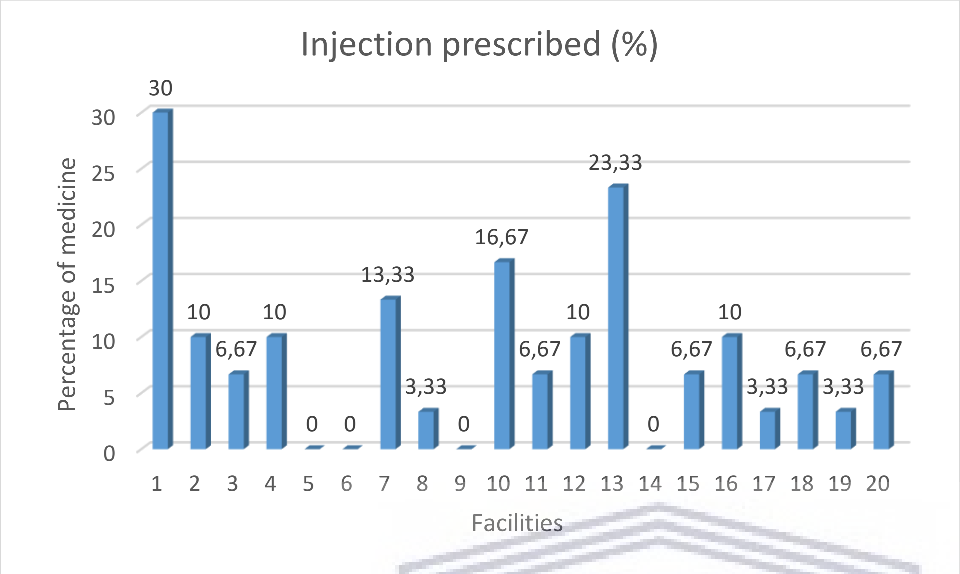
Out of 600 prescriptions evaluated, 28.17% (*SD* = 8.59) of the patients encountered, received one or more antimicrobial from the facilities, some with a minimum of 13.33%, and others with maximum of 43.33%. At least 11 facilities had the percentage of antimicrobials received per individual encounter, below the optimal value of less than 30% (Table 4.2 and figure 4.3).

Figure 4.3: Percentage of antimicrobial prescribed per encounter



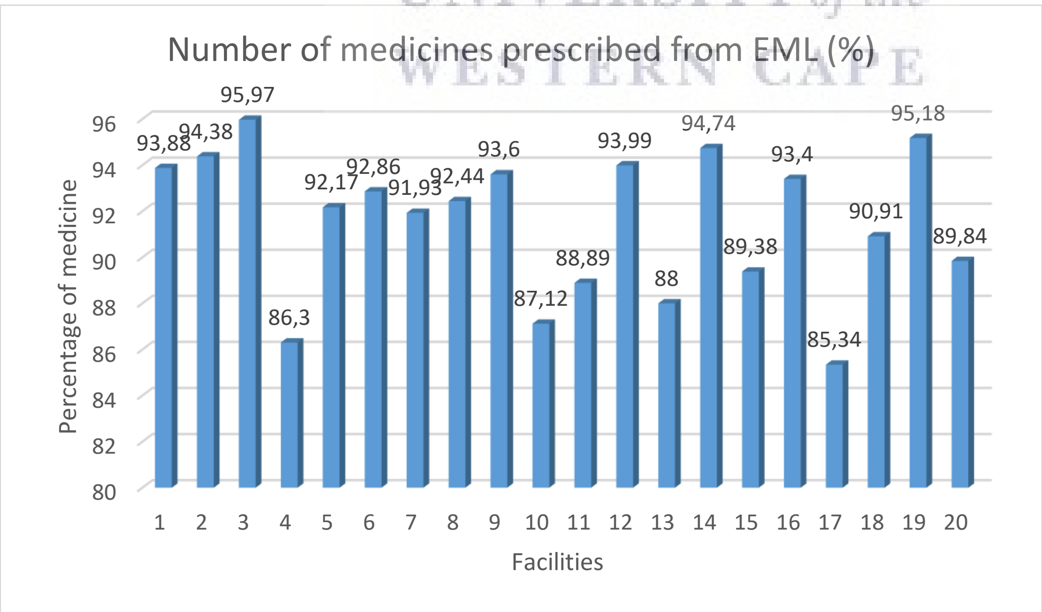
Injections were prescribed to 8.33% (*SD* = 7.64) of the patients, on average; however, 3 facilities encountered no patients, who received injections, while at other facilities, 30% of the patients received injections. More than 10% of the patients received an injection at 8 facilities (Table 4.2 and figure 4.4.).

Figure 4.4: Percentage of injection prescribed



Of all the medicines prescribed, 91.52% were prescribed from the EML (8.48% of medicines prescribed were non-EML), with a standard deviation of 3.05. At some facilities only 85.34% of the medicines prescribed were from the EML, while at others, 95.97%. This indicate that none of the facilities had 100% of all medicines prescribed from the EML (Table 4.2 and figure 4.5).

Figure 4.5: Percentage of medicines prescribed from EML



The degree of rational prescribing was determined by calculating the IRDP, and its total (Table 4.4). The index of non-polypharmacy was 0.44, which was much lower than the optimal index of

1. Only 2 facilities had an index greater than 0.5, which equals a 50% level of non-polypharmacy prescribing. The index for prescribing medicine by its generic name was 0.44. Only 8 of the 20 facilities had an index greater than 0.5, with the highest of 0.60, and the lowest of 0.18. The index of rational prescribing of antimicrobial was 0.93, which was very close the optimal index of 1. The lowest index of rational antimicrobial prescribing was 0.69, with 8 facilities having an index lower the optimal index of 1. The index for the safe use of injections was 0.91, and only 4 facilities had an index below the optimal index of 1, with lowest being 0.33. The prescribing of medicine from the EML was 0.92. All the facilities were observed to be below the optimal value of 1, with the lowest index of 0.85, and the highest of 0.96. The total IRDP was 3.64, which was much lower than the optimal level of 5.

Table 4.2: Prescribing indicators per facility

Facility	Average number of medicines prescribed per encounter	Antimicrobial prescribed (%)	Injection prescribed (%)	Number of medicines prescribed in generic/INN (%)	Number of medicines prescribed from EML (%)
1	4.90	43.33	30.00	50.34	93.88
2	2.97	36.67	10.00	35.95	94.38
3	4.97	23.33	6.67	45.64	95.97
4	4.87	26.67	10.00	29.45	86.30
5	3.83	16.67	0.00	46.09	92.17
6	3.73	16.67	0.00	43.75	92.86
7	5.37	36.67	13.33	41.61	91.93
8	3.97	26.67	3.33	59.66	92.44
9	5.20	26.67	0.00	43.58	93.60
10	4.40	13.33	16.67	54.54	87.12
11	3.90	36.67	6.67	41.03	88.89
12	4.43	16.67	10.00	49.62	93.99
13	3.30	23.33	23.33	33.00	88.00
14	3.80	26.67	0.00	51.75	94.74
15	3.76	33.33	6.67	34.51	89.38
16	3.53	30.00	10.00	53.77	93.40
17	3.87	36.67	3.33	37.07	85.34

18	4.40	26.67	6.67	51.51	90.91
19	5.53	23.33	3.33	18.07	95.18
20	4.27	43.33	6.67	54.69	89.84
Total	**4.25**	**28.17**	**8.33**	**43.78**	**91.52**
Standard deviation	**2.54**	**8.59**	**7.64**	**9.96**	**3.05**
Optimal value	**1.6-1.8**	**<30**	**<10**	**100**	**100**
Optimal IRDP*	**1**	**1**	**1**	**1**	**1**

* **Index of Rational Drug Prescribing**

Table 4.3: Frequencies of number of medicines prescribed per encounter

Number of medicine prescribed per encounter	Frequency of number of medicine prescribed	Percentage	Cumulative percentage
1	52	8.70	**8.70**
2	109	18.20	**26.90**
3	117	19.50	**46.40**
4	107	17.80	**64.20**
5	62	10.30	**74.50**
6	55	9.20	**83.70**
7	26	4.30	**88.00**
8	29	4.80	**92.80**
9	16	2.70	**95.50**
10	11	1.80	**97.30**
11	6	1.00	**98.30**
12	6	1.00	**98.30**
13	3	0.50	**99.80**
17	1	0.20	**100.00**

Table 4.4: The index of rational drug prescribing (IRDP)

Facility	Index of non-polypharmacy	Index of generic name	Index of rational antimicrobial	Index safety Injection	Index of EML	Total Index
1	0.37	0.5	0.69	0.33	0.94	2.83
2	0.61	0.36	0.82	1.00	0.94	3.73
3	0.36	0.46	1.00	1.00	0.96	3.78
4	0.37	0.29	1.00	1.00	0.86	3.52
5	0.47	0.46	1.00	1.00	0.92	3.85
6	0.48	0.44	1.00	1.00	0.93	3.85
7	0.34	0.42	0.82	0.75	0.92	3.25
8	0.45	0.60	1.00	1.00	0.92	3.97
9	0.35	0.44	1.00	1.00	0.94	3.73
10	0.41	0.54	1.00	0.60	0.87	3.42
11	0.46	0.41	0.82	1.00	0.89	3.58
12	0.41	0.50	1.00	1.00	0.94	3.85
13	0.55	0.33	1.00	0.43	0.88	3.19
14	0.47	0.52	1.00	1.00	0.95	3.94
15	0.48	0.35	0.90	1.00	0.89	3.62
16	0.51	0.54	1.00	1.00	0.93	3.98
17	0.47	0.37	0.82	1.00	0.85	3.51
18	0.41	0.51	1.00	1.00	0.91	3.83
19	0.33	0.18	1.00	1.00	0.95	3.46
20	0.42	0.55	0.69	1.00	0.90	3.53
Total	**0.44**	**0.44**	**0.93**	**0.91**	**0.92**	
IRDP	**3.64**					

4.4. Facility indicators

The results in the facility indicators revealed the capacity of each facility to provide quality health care, based on the availability of the latest medicine information resources, facility formulary, treatment protocols, and multidisciplinary forum, which deals with medicine related issues (Table

4.5 and Annexure G). A total of 20 public hospitals of the 42 Limpopo Province public hospitals were included in this current study. All the included health facilities had reportedly established and implemented a Pharmacy and Therapeutic Committee (PTC), which met on a monthly basis. The availability of a hospital formulary, or Essential Medicine List (EML) was reported to be available at 17 facilities, with 11 of the 17 facilities adhering to the national Standard Treatment Guideline (STG), which was last revised 4 to 6 years prior to the date on which this current study was conducted. None of the included facilities reported using the adult hospital STG/EML, revised in 2015 (which is latest hardcopy). The paediatric hospital STG/EML, revised in 2013 was reportedly used by 6 facilities, and regarded as acceptable. The Primary Health Care (PHC) STG/EML was reportedly used in 5 facilities, and regarded as unacceptable, because the study was conducted at hospital level. Only 5 facilities had adopted the provincial formulary, which was officially launched in 2017, and 1 facility had its own hospital formulary, recently updated in 2018 (Table 4.5, 4.6, and Annexure G).

The availability of a STG for infectious diseases was reportedly available at 14 facilities. One facility's STG was revised in 2018, referring to its own hospital formulary, 2 facilities adhered to the Limpopo provincial formulary, which were regarded as acceptable. The hospital STG/EML for adults, last revised 6 years earlier, was used by 2 facilities, and considered unacceptable. The STG/EML for paediatrics, last revised 5 years earlier, was reportedly used by 2 facilities, and considered acceptable, as it was the latest hardcopy revision. The Primary Health Care (PHC) STG/EML, updated 4 years earlier, was used by 4 facilities, with all referring to hard copies. The availability of standards or protocols for surgical prophylaxis, using antimicrobials, was observed at 50% of the facilities, while all facilities disclosed having a guideline for infection control.

The degree to which facilities were prepared to provide quality healthcare services, was measured by the Index of Rational Facility Specific Drug Use [IRFSDU] (Table 4.5). The study findings revealed that all the facilities had an index of 1, for existence of a PTC. The index for the availability of an acceptable hospital formulary/EML copy was 0.60, which implied that the degree of all facilities with the latest copy of a formulary/EML was 60%. The availability of an acceptable STG for infectious disease had an index of 0.35, which was much lower than the optimal index of 1, indicating that the percentage of all facilities with a STG for infectious diseases was 35%.

All facilities were expected to have standard protocol for surgical prophylaxis, using antimicrobials to prevent surgical site infection (SSI); however, in this current study, it was observed that the availability of surgical protocol had the index of 0.5 which was lower than optimal index. In order to contain the spread of infections, each facility should have a guideline for infection control and prevention, which must be accessible to all healthcare providers. In this current study, the index for the availability of an infection control guideline was 1 (100%). The total IRFSDU that was obtained by adding up all five mentioned indices, was 3.45, which was lower than the optimal index of 5.

Table 4.5: WHO/INRUD facility indicator results

Questionnaire	Yes (%)	No (%)	IRFSDU*
Does the hospital have PTC?	100.00	0.00	1.00
Availability of hospital acceptable formulary or EML	60.00	40.00	0.60
Availability of acceptable STG for infectious diseases	35.00	65.00	0.35
Availability of protocol for surgical prophylaxis with antimicrobial	50.00	50.00	0.50
Availability of infection control guideline	100.00	0.00	1.00
Total IRFSDU			3.45

***Index of Rational Facility Specific Drug Use**

Table 4.6: The STG/EML and/or formulary used by facilities

Facility	STG/EML or facility formulary revision year	Appropriate (yes/no)
1	2014 (PHC)	No
2	None	No
3	2014 (PHC)	No
4	2014 (PHC)	No
5	2017 (Provincial formulary)	Yes
6	2017 (Provincial formulary)	Yes
7	2013 (Paediatric)	Yes
8	2012 (Adult hospital)	No
9	2013 (Paediatric)	Yes
10	2013 (Paediatric)	Yes

11	2014 (PHC)	No
12	2017 (Provincial formulary	Yes
13	None	No
14	2018 (Facility formulary)	Yes
15	2013 (Paediatric)	Yes
16	2017 (Provincial formulary)	Yes
17	2013 (Paediatric)	Yes
18	2014 (PHC)	No
19	2017 (Provincial formulary)	Yes
20	2013 (Paediatric)	Yes
Percentage of facilities with appropriate STG/EML or formulary		**60%**

STG/EML – Standard treatment guideline and essential medicine list

PHC – Primary health care

4.5. Antimicrobial use indicators

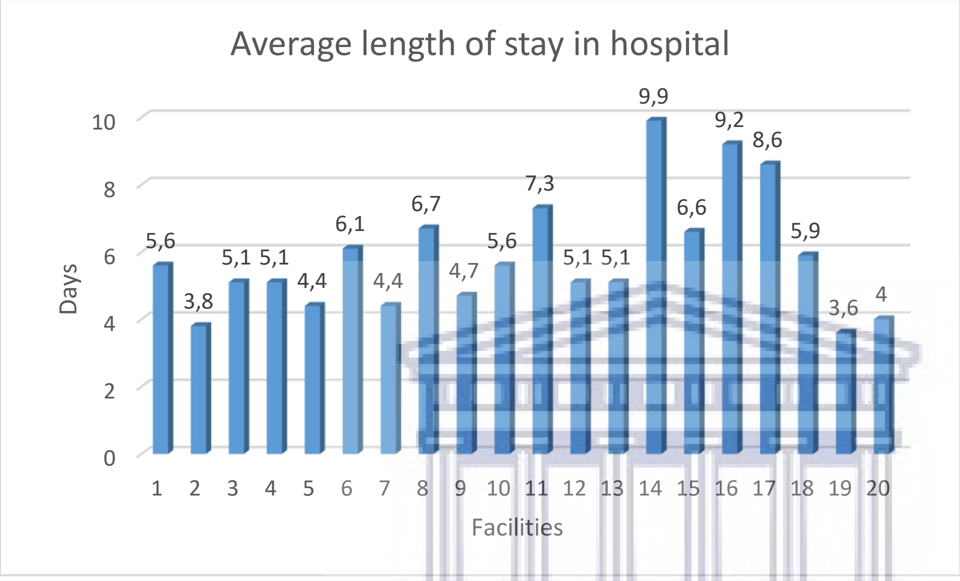
The antimicrobial use indicators presents retrospective antibiotics prescribing results of inpatients, involved in this current study, focusing on whether the antibiotics were prescribed in accordance with treatment guidelines or protocols. Additionally, the patients' length of stay in hospital, the number of patients, admitted due to pneumonia, in how many cases culture sensitivity tests were done, as well as whether the prescribed antibiotics were from the EML, and prescribed by their generic names, were explored, to determine the average number of antimicrobials prescribed per inpatient (Table 4.7 and 4.8).

To determine the quality of patient care for most common infectious diseases, pneumonia was used as a common infectious disease that would result in a patient's hospital admission. The management of patients, admitted because of pneumonia, was assessed to determine whether their admissions were in accordance with the national EML clinical guide app, and the South African guideline for the management of community-acquired pneumonia in adults (Bolyes et al., 2017), focusing on antimicrobial of choice, dosage and frequency. For this current research, a retrospective study was conducted with admitted patients, who received antimicrobials during their hospital stay. Ten (10) patients per facility, totalling 200 patients, were included in this current study. The patients included were aged 1 to 111 years, with a mean age of 32.08 (SD = 26.56), an

IQR of 31.14 (4 – 52.75), a skewness of 0.43 (SE = 0.17), and a kurtosis of -0.81 (SE = 0.34), comprising 59.5% female and 40.5% male.

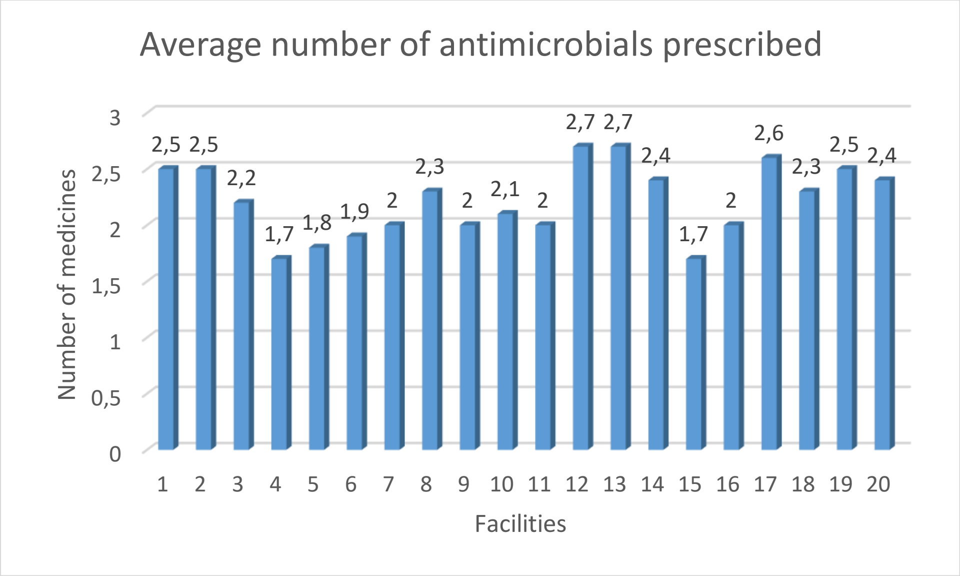
The average hospital stay was 5.18 (SD = 5.13) days, with a minimum and maximum stay of 1 day and 30 days, respectively, a skewness of 2.32 (SE = 0.17), a kurtosis of 6.04 (SE = 0.34), and an IQR = 5.00 (3.00 -7.00) days (Table 4.7 and figure 4.6.).

Figure 4.6: Average length of stay in hospital



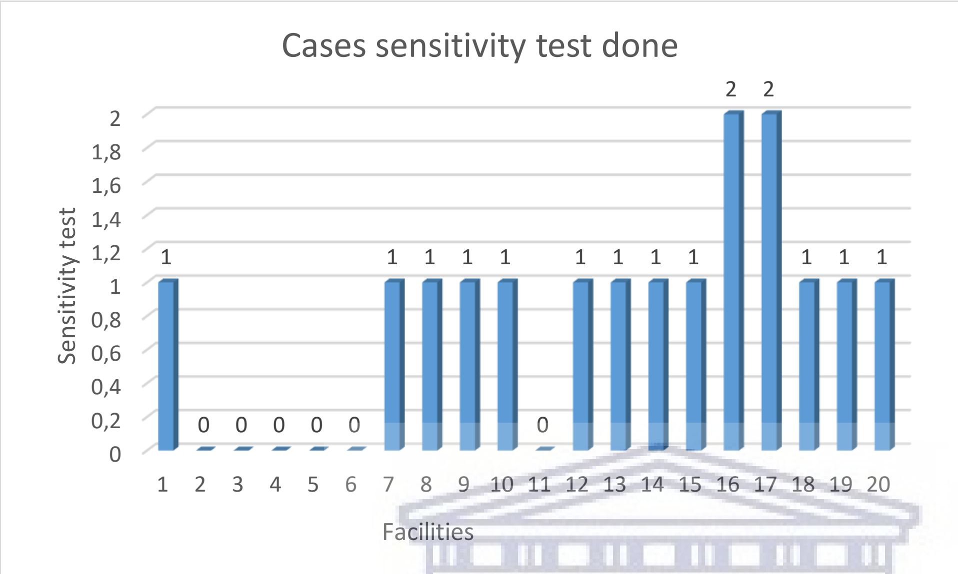
The average number of antimicrobial prescribed per patient was 2.19 (SD = 0.32), with a minimum of 1.00 and a maximum of 5.00 antibiotics combined. It had a skewness of 0.57 (SE = 0.17), a kurtosis of 0.31 (SE = 0.34), and an IQR = 2.00 (2.00 – 3.00) see figure 4.7 and table 4.7.

Figure 4.7: Average number of antimicrobials prescribed



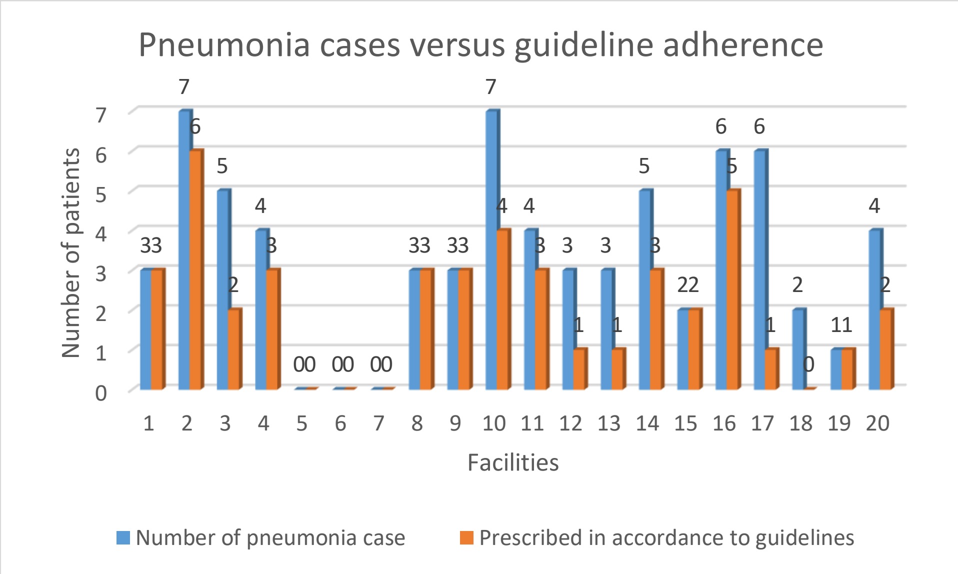
Of the 200 cases included in this current study, only 16 (8%) culture sensitivity tests were conducted (Table 4.7 and figure 4.8).

Figure 4.8: Number of sensitivity test done



The total number of patients admitted because of pneumonia were 68, of which only 43 (63.2%) were treated in accordance with treatment guidelines (Table 4.7 and figure 4.9). Of the 20 facilities included, only 3 facilities had zero pneumonia cases among their 10 patients included in this current study, while 6 facilities had more than 5 of their 10 inpatients admitted due to pneumonia. The children, 5 years and younger, received the combination of ampicillin and gentamycin, and discharged with amoxicillin, in accordance with clinical guidelines. The children's treatment that did not comply with clinical guidelines, was the frequency of ampicillin that was administered at 8 hourly, instead of 6 hourly intervals. The adults' treatment that did not comply with clinical guidelines, was the incorrect combination of injectable antimicrobials, for example, ceftriaxone and metronidazole, ceftriaxone and amoxicillin/clavulanic acid, ceftriaxone and ampicillin, and the unnecessary use of metronidazole (See Annexure I). The culture sensitivity test was conducted in 9 (13.24%) of the 68 pneumonia cases. Out of 68 pneumonia cases, 30 (44.12%) patients were admitted for more than 3 days and received intravenous antibiotics until they are discharged, without culture sensitivity test, or a switch to oral administration, which indicates that switching from intravenous to oral was seldom executed.

Figure 4.9: Patients with pneumonia and treated according to guideline.



The percentage of antibiotics prescribed by generic name was 33.33% (SD = 10.56), with minimum of 11.76%, and maximum of 60%. Only 1 facility had more than 50% of the antimicrobials prescribed by generic names (Table 4.7 and figure 4.10). Ampicillin (mostly prescribed), azithromycin, cloxacillin, doxycycline and gentamycin were the only antimicrobials prescribed by their generic names. Rocephin® (mostly prescribed following ampicillin), Augmenting®, Flagyl®, Ciprobay® and Bactrim® were branded names prescribed (Table 4.8). The average percentage of antimicrobial prescribed from EML was 100% (SD = 1.54), and only one facility had 10% of the antimicrobials prescribed that were non-EML (Table 4.7 and figure 4.10), namely the amoxicillin injection, while the patient received the ampicillin injection (Table 4.8).

Figure 4.10: Percentage of antimicrobial prescribed by generic name and on EML

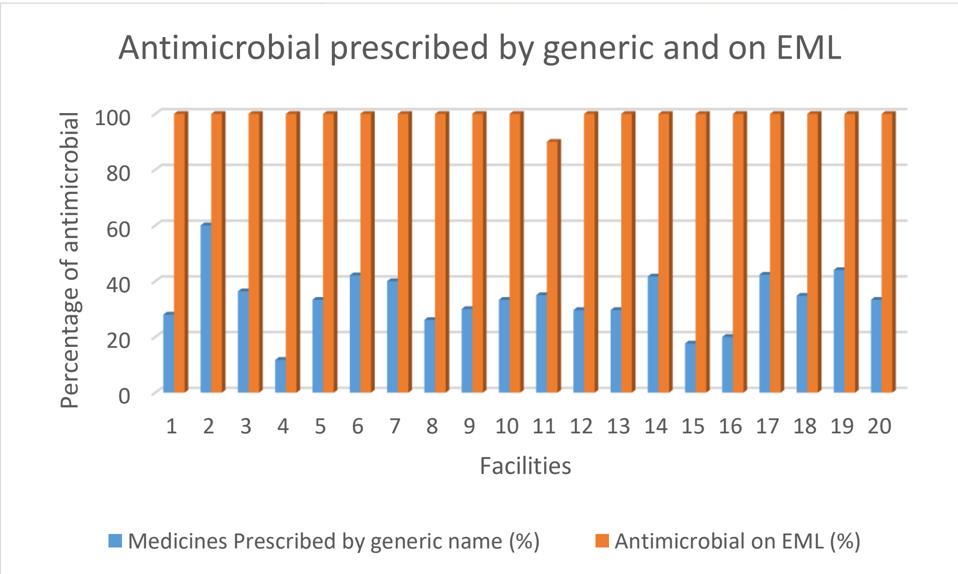


Table 4.7: Antimicrobial use indicators per facility

Facilities	Number of pneumonia case	Average number of days in hospital	Cases sensitivity test done	Average number of antimicrobials prescribed	Prescribed in accordance to guidelines	Medicines Prescribed by generic name (%)	Antimicrobial on EML (%)
1	3	5.6	1	2.5	3	28.00	100
2	7	3.8	0	2.5	6	60.00	100
3	5	5.1	0	2.2	2	36.36	100
4	4	5.1	0	1.7	3	11.76	100
5	0	4.4	0	1.8	0	33.33	100
6	0	6.1	0	1.9	0	42.11	100
7	0	4.4	1	2	0	40.00	100
8	3	6.7	1	2.3	3	26.09	100
9	3	4.7	1	2	3	30.00	100
10	7	5.6	1	2.1	4	33.33	100
11	4	7.3	0	2	3	35.00	90
12	3	5.1	1	2.7	1	29.63	100
13	3	5.1	1	2.7	1	29.63	100
14	5	9.9	1	2.4	3	41.67	100
15	2	6.6	1	1.7	2	17.64	100
16	6	9.2	2	2	5	20.00	100
17	6	8.6	2	2.6	1	42.31	100
18	2	5.9	1	2.3	0	34.78	100
19	1	3.6	1	2.5	1	44.00	100
20	4	4	1	2.4	2	33.33	100
Overall results	**68**	**5.81**	**16**	**2.19**	**43**	**33.33**	**100**
SD*		**5.13**		**0.89**		**10.56**	**1.54**

***Standard deviation**

Table 4.8: List of frequently use antimicrobial

Name of antimicrobial and administration route	Frequency	Generic name (Yes/No)	On EML (Yes/No)
Amoxicillin intravenous	1	Yes	No
Amoxicillin oral	6	Yes	Yes
Amoxyl® oral	49	No	Yes
Ampicillin intravenous	88	Yes	Yes
Augmentin® intravenous	42	No	Yes
Augmentin® oral	33	No	Yes
Azithromycin oral	15	Yes	Yes
Azithromycin intravenous	1	Yes	Yes
Bactrim® oral	4	No	Yes
Bactrim® intravenous	1	No	Yes
Benzylpenicillin intramascular	1	Yes	Yes
Cefazolin intravenous	3	Yes	Yes
Cefzol® intravenous	2	No	Yes
Ceftriaxone intravenous	4	Yes	Yes
Rocephin® intravenous	59	No	Yes
Chloramex® ointment	2	No	Yes
Ciprobay® oral	10	No	Yes
Cloxacillin oral	11	Yes	Yes
Cloxacillin intravenous	5	Yes	Yes
Doxycycline oral	1	Yes	Yes
Flagyl® intravenous	60	No	Yes
Flagyl® oral	20	No	Yes
Gentamycin intramuscular	1	Yes	Yes
Gentamycin intravenous	18	Yes	Yes
Pen VK®	1	No	Yes

CHAPTER FIVE

DISCUSSION

5.1. Introduction

The rational use of medicine is a worldwide concern and a current topic of interest. It is important to promote the rational use of medicine for economic and clinical benefit. When medicines are not used correctly, negative consequences affect patient health, and limited financial resources are wasted. Each country and facility needs to evaluate and understand their current medicine usage. In this current study, the researcher used the World Health Organisation and International Network for Rational Use of Drug (WHO/INRUD) core drug indicators and antimicrobial use indicators in hospital to evaluate the current medicine use. Similar studies that were conducted in South Africa and other countries across the world, as well as eleven articles were reviewed to compare with this current study, to assess whether the findings depict an improvement in the rational use of medicine (See Table 3.2).

5.2. Facility Indicators

The WHO, as well as the South African National Drug Policy (NDP) recommend the establishment and implementation of a Pharmacy and Therapeutic Committee (PTC) at facility and provincial level. All the facilities included in this study were reported to have an active PTC that met on a monthly basis, which implied that one of the WHO twelve core interventions to promote RMU had been achieved. The main goal of the PTC is to ensure that patients receive cost-effective and quality healthcare, by developing and implementing standard treatment protocols, and a formulary list (Holloway & Green, 2003). The PTC promotes more RMU through the provision of medicine related education; therefore, if the facilities PTCs are functional, it implies that health professionals are receiving medicine-related training, and medicines are being used more rationally.

Each facility PTC could either develop its own formulary list, or adopt a national/provincial one. In this current study, 17 facilities reportedly had a hospital formulary, or Essential Medicine List (EML), and of the 17, only 1 facility had recently updated (in 2018 same year of data collection) its own formulary. For the first time, the Limpopo Province had developed and officially launched its provincial formulary in 2017; however, only 5 (25%) of the facilities involved in this current study, reportedly, had adopted it. Of the 5 facilities that had adopted the provincial formulary, three were regional hospitals, and two, district hospitals, which might indicate the differences in priorities given to different levels of facilities. The World Health Organization (WHO) formulary model has minimum requirements to be included in a formulary, namely, medicine generic names, dosage form and strength, main indication, pharmacokinetics, contraindications, precautions, dosage schedule, adverse effects, medicine information, instructions and warnings (WHO, 2004). The Limpopo provincial formulary did not meet the minimum requirements of the WHO formulary model, because it only contain, medicine generic name, dosage form, strength and main indication, which it resembles the WHO model of the Essential Medicine List (WHO, 2017b). The South African Medicine Formulary (SAMF) is one among the best national formularies developed, and each facility is supposed to have a similar formulary that contains medicine dosages and safety profiles (MSH, 2012). The fact that not all facilities had a copy of the provincial formulary, indicated either poor acceptance of this formulary, due to the poor/non-involvement of end-users in the development process, or poor dissemination, resulting in the lack of knowledge of its existence. This might also indicate poor communication between the facility, district, and provincial PTCs, because once the formulary was launched, its usage and availability had to be enforced (MSH, 2012).

Additionally, the availability of an EML is one of the most cost-effective interventions that could improve the supply of medicine, rational prescribing, and reduced cost (MSH, 2012). It is recommended that the Standard Treatment Guideline (STG) and EML should be updated regularly, and not only after a two yearly period, but continuously (WHO, 2001). The South African primary healthcare [PHC] STG and EML have been revised 6 times [1996, 1998, 2003, 2008, 2014, and 2018], the adult hospital STG and EML revised 4 times [1998, 2006, 2012, and 2015], and the paediatric hospital STG and EML revised 3 times [1998, 2006, and 2013] (Perumal-Pillay & Suleman, 2016). The latest PHC STG and EML revision, in September 2018, occurred during this current study; therefore, the assumption was that it had not reached the facilities yet. The STG and EML in South Africa are available on mobile phone apps; however, none of the facilities, involved in this current study, were reportedly using these apps. This might be a sign that very few healthcare providers were aware of the existence of these apps, as a result of poor communication, while many rural areas have network coverage challenge, which might also be a barrier to the use of the apps.

In this current study, 10% of the facilities were using a STG and EML for adults, revised 6 years before (in 2012, while the latest revision was 3 years before in 2015), 20% of the facilities were using a STG and EML for paediatrics, revised 5 years before (which is latest available hardcopy), and 20% of the hospitals were using a STG and EML, intended to be used at PHC level, also revised 4 years before (Annexure G). This indicated that the healthcare providers did not have access to up-to-date medicine information/guidelines, and that, in general, the dissemination of guidelines was still a challenge. Pharmacists, as custodians of the medicines, are expected to be the source of medicine information; therefore, the availability of a STG in the pharmacy would indicate that the prescribers were provided with the latest, unbiased, evidence-based medicine information (Essack et al., 2011). The findings of this current study revealed that pharmacists were using STGs that had been revised 4 to 6 years previously, indicating they were not in possession of recent information; therefore, the prescribers and other healthcare providers were not provided with the latest medicine information.

When healthcare professionals were interviewed for the availability of the hospital formulary/EML, their responses were as if the researcher was referring to a STG, which implied they were unable to differentiate between the two. This supports the notion that the EML and STG must be developed with the involvement of the end-user, including healthcare providers, as well as society, taking into account the healthcare sector and the societal perspective, and must be launched, formally, by teaching end-users how to use them (WHO, 2004).

Antibiotic prophylaxis is one of the cost-effective interventions for the prevention of surgical-site infection; therefore, hospitals should ensure the appropriate use of surgical prophylaxis (Bonello & Stafrace, 2016). Regarding a STG for infectious diseases, all the facilities reported using a STG & EML, as well as a provincial formulary. The availability of infectious control guidelines were reportedly available in 95% of the facilities; however, 55% of the facilities did not have a protocol for surgical prophylaxis, using antimicrobials. Additionally, most pharmacists had never seen the infection control guideline, as they had to approach the infection control nurse, to inquire about the availability of such a guideline. The most common cause of inappropriate antibiotic prophylaxis, included inappropriate timing (too late, or too early) and inappropriate duration (Lim et al., 2015). A study conducted in Italy revealed that only 18.1% cases of perioperative antibiotic prophylaxis were appropriate, while the timing of administration were appropriate in 53.4% (Napolitano et al., 2013). Evidently, there is a need to continuously encourage and educate pharmacists, as well as pharmacy students, to participate in the decision making of individual patients, including the selection of antimicrobials, used in surgical procedures.

5.3. Prescribing Indicators

Polypharmacy is one of the factors that contributes to the irrational use of medicines by prescribers and patients, as it leads to a high incidence of adverse drug reaction (ADR), medicine interaction, increased hospital length of stay [LOS], readmission, and consequently, increased healthcare cost (Salwe, Sundaram, & Bahurupi, 2016). The definition of polypharmacy is variable, and does not take into account the existence of comorbidity, making it difficult to evaluate appropriateness and safety in the clinical setting (Masnoon, Shakib, Kalisch-Ellet, & Caughey, 2017); however, to improve safety and appropriate prescribing, it is important to assess polypharmacy. The WHO recommends an optimal average number of medicines prescribed per encounter of 1.6 - 1.8; however, the findings of this current study revealed an average of 4.25 (2.9 - 5.53), which indicates that polypharmacy was being practiced.

The findings of this current study is similar to that of a study conducted in Ghana, which revealed an average number of medicines prescribed per encounter of 4.1 (Table 2.1). In Ghana, patients equate quality healthcare with the number of medicines received, implying that the more medicines prescribed, the better the service delivered. However, Ghana is one of the countries to implement a National Health Insurance (NHI) system that uses the approach of fee-for-service, which appears to be the contributing factor behind the prescribing of more medicines, to generate more revenue for the facilities (Ahiabu et al., 2016). South Africa needs to implement a system that would prevent unnecessary polypharmacy, before the full implementation of the NHI. The mean age of this current study was 43.85, and the findings of most studies have revealed that increased age is associated with comorbidities, resulting in more medicine being prescribed (Van Heerden et al., 2016). However, an elderly population is more prone to ADR, easily forgetting how to take their medication; therefore, a need exists to monitor the appropriate use of medicine by this population, as well as ensure correct management of their acute and chronic conditions (Spinewine et al., 2005).

The findings of this current study revealed an increased tendency to prescribe more medicines to patients, compared to baseline studies conducted in South Africa, namely, 1996 to 1998, 2003, and the study comparing Western Cape and Limpopo Province in 2005, in which the average number of medicines prescribed per encounter were 2.5, 2.2, 3.0 and 3.4, respectively (Table 2.1). The increase in the average medicines prescribed per encounter, from 1996 to the present, may be due to the expectation that multi-morbidity would rise, as a result of the population growing older, and developing multi-morbidity (Masnoon et al., 2017), although the majority of patients included in this current study were 30 to 49 years of age. The result of polypharmacy of this current study is twice as high as studies conducted in Ethiopia and other countries (Table 2.1). The index of non-polypharmacy was observed to be 0.44, which was lower than optimal value of 1, and the value of 0.88 observed in Tanzania (Irunde et al., 2017). This index of non-polypharmacy indicates that 44% of the total prescriptions, comprised a reasonable number of medicines per individual, per encounter.

The South African National Drug Policy (RSA, NDOH, 1996) encourages the use of generic medicines, while the Medicine and Related Substance Act 101 of 1965 (RSA, NDOH, 1997) states that pharmacists must always inform patients of the availability of generic medicines, and their advantages. In this current study, only 43.78% of medicines were prescribed in generic names, which implies that more than 50% of the medicines were still prescribed in their branded names. In South Africa, the pharmacy week theme of 2013 was, *Towards Quality Care together*, with a sub-theme of, *Understand Generic Medicine*, which was aimed at educating patients on the benefits of generic medicines. This might indicate that the encouragement to use generic medicines was more focused on patients and undergraduate doctors, while the prescribers in practice were neglected; consequently, the prescribers prescribed less medicines with generic names.

This current study's finding percentage of medicines prescribed in generic names, was lower than in other countries, namely, Sierra Leone, China, Ghana, Tanzania, Pakistan, Ethiopia and Egypt with 71.0%, 64.12%, 79.2%, 95.7%, 71.6%, 98.7 and 95.4%, respectively (Table 2.1). Although there is an improvement in generic prescribing, compared to baseline studies in South Africa, from 36% to 43.78%, many campaigns, education, encouragement, and re-enforcement mechanisms need to be in place to reach the optimal value of 100%, and an Index of Rational Drug Use (IRDP) of 1. The index of generic prescribing was 0.44, which is lower than studies conducted in Egypt, China and Sierra Leone, with values of 1, 0.64, and 0.71, respectively (Akl et al., 2014; Dong et al., 2011; Cole et al., 2015).

The over prescribing of antimicrobials is one of the factors that fuel the emergence of antimicrobial resistance (AMR) making it more difficult, and expensive to treat common bacterial infections (WHO, 2014a). The percentage of antimicrobials prescribed per encounter was 28.17%, which is slightly higher than the WHO recommended 20.0 to 26.8%, but lower than the optimal value of <30 used in this current study. The percentage of antimicrobial use in this current study was higher than studies conducted in Brazil and India, with 21.3% and 22%, respectively, but lower than studies conducted in African countries, namely, Ghana, Tanzania, Pakistan, Ethiopia and Egypt, with 59.9%, 67.7%, 48.9, 58.1%, and 39.2% respectively (Table 2.1). There is a great improvement of antimicrobial prescription per encounter, compared to a study conducted in South Africa (Western Cape and Limpopo Province) in 2005, which were at 53.2% and 56.7%, respectively (Table 2.1); however, this reduction in antimicrobial usage does not guarantee that the rational use of antimicrobials has improved. Therefore, there is need to implement continuous active surveillance, control, and restriction of antimicrobial medicines, and the economic impact of programmes that monitor antimicrobial usage, such as the Antimicrobial Stewardship Program (ASP), needs to be evaluated in both healthcare and societal perspectives (WHO, 2014a). In this current study, the degree of rational antimicrobials, as determined by the IRDP, was observed to have an index of 0.93, which is higher than 0.40, observed in Sierra Leone (Cole et al., 2015), and 0.62 in China (Dong et al., 2011).

One of the most preferable modes of medicine administration is the injection method, and its use, reportedly, is influenced by patients' and healthcare providers' beliefs (World Health Organization [WHO], (2004b. However, the excessive use of injections, may lead to transmission of blood borne diseases (Ofori-Asenso & Agyeman, 2016). In this current study, the percentage of injections administered per encounter was 8.33%, which is lower than the optimal level of <10. The index of the safe use of injections in this current study was 0.91. According to the findings, the percentage of injection usage in this current study, was exactly the same as the percentage observed in a study conducted in Brazil, but higher than studies conducted in Nepal and India, which were 3.44% and 7%, respectively (Table 2.1). There was a decrease in injection use, when compared to a South African baseline study in 1996-1998, and a Limpopo Province survey in 2005, but higher than a South African survey conducted in 2003, and a Western Cape Province survey in 2005 (Table 2.1). This implies that the monitoring of injection usage, as well as the healthcare awareness of the negative impact of the excessive use of injections, need to be emphasised, continuously.

The essential medicine concept is aimed at bridging the gap of medicine availability and accessibility, by selecting a limited number of medicines to meet the needs of the population. Ideally, medicines on the Essential Medicine List (EML) should be procured, prescribed, and dispensed to patients (Ofori-Asenso & Agyeman, 2016). Medicines are selected to the EML, based on evidence-based efficacy and safety, as well as availability and affordability, implying that, in order to prescribe more rationally, prescribers have to prescribe medicines from the EML (WHO, 2004a). In this current study, the researcher observed that 92.46% of the medicines prescribed, were from the EML, with an index of 0.92, which is lower than the optimal value of 100% (Table 3.2). India has many pharmaceutical companies (Aravamuthan et al., 2017); therefore, it is not surprising to observe the lowest use of generic named medicines (2.5%). However, 99.8% of those medicines prescribed, were from their EML (Table 2.1).

There is an improvement in prescribing medicines from the EML, compared to baseline studies conducted in South Africa, as indicated in Table 2.1. The index of prescribing medicines on the EML was 0.92, which is lower that the optimal value of 1, and the index of 0.97 observed in Tanzania (Irunde et al., 2017), but higher than the index of 0.68 observed in China (Dong et al., 2011). The total IRDP was 3.64, lower than optimal value of 5; however, higher than total IRDP observed in China (2.71), Sierra Leone (3.32), and lower than Tanzania (3.81).

5.4. Antimicrobial use Indicators

When antimicrobials are irrationally used, the results could be prolonged hospital stays, increased re-admissions, ADR, increased resistance and health care costs (WHO, 1993). The Global Action Plan on antimicrobial resistance encourages optimisation of antimicrobial use, strengthening knowledge through evidence-based research and active surveillance; however, it is still a challenge to determine antimicrobial consumption data in low-resourced settings (Schellack et al, 2017). Service providers should strive to optimise antibiotic use, reduce resistance, and improve patient outcomes (Silva & Silva, 2015).

The findings of this current study revealed the average hospital stay as 5.1 days. The average number of antibiotics prescribed per patient was 2, which indicates that monotherapy was hardly preferred. Of the 200 cases included in this current study, only 16 culture and sensitivity tests were conducted to narrow the treatment to the identified agent, which might also be a reason why more than one antibiotic was prescribed per patient, as conducting fewer microbiological investigations, could contribute to longer hospital stays, and unnecessary combinations of antibiotics. The findings of a study conducted by Lim et al. (2015), with 129 patients in Malaysia, revealed an average number of 4.6 antibiotics per patient, while only 34% received appropriate antibiotic therapy. According to Brink et al. (2016), there is no evidence that a combination of antibiotics could result in a synergetic effect, and reduce the chances of AMR. However, Tammer et al. (2012) argue that effective therapy for patients, who are infected with multi-drug resistant organisms, may be delayed initially, which increases the risk of mortality, which could be avoided, with the treatment of an additional agent, once the antibiogram is received, and treatment can be narrowed.

Delayed appropriate therapy is associated with an increased length of stay [LOS], inflated total in-hospital costs, and the risk of hospital mortality, regardless of the patient's susceptibility status (Bonine et al., 2019).

Adherence to local, or international guidelines, is one of the key strategies of promoting the rational prescribing of medicine; however, despite a number of published guidelines, to optimise the choice of antimicrobial agents and therapy duration, there is still a disparity in prescribing practice (Gupta et al., 2011). In this current study, of the 200 cases, 68 patients were diagnosed with pneumonia, and 63.24% (43) were prescribed in accordance with the STG for infectious diseases, which is lower than the optimal value of 100%. Those, who were not prescribed in accordance with the STG, received the incorrect combination of antibiotics (ceftriaxone and amoxicillin/clavulanate simultaneously), the incorrect dosage, wrong choice of antibiotic agent (unwarranted addition of metronidazole), and a prolonged use of injectable antibiotics (given until patient discharge day), without antimicrobial sensitive results. The findings of a study conducted by Bonello and Stafrace (2016) revealed that, of the 110 patients undergoing general surgery in Mater Dei hospital, Zimbabwe, only 9.3% were completely adhering to the local STG. In another study conducted at a private hospital in Kwazulu-Natal Province, South Africa, the findings revealed that, of the 131 cases of patients with indications for antibiotics, only 70.2% were prescribed according to the STG, and microbiological investigations were conducted on 61.2%, of which in 70.8% of the cases, de-escalation was indicated; however only 13.1% de-escalation was noted (Chunnilall et al., 2015). In addition, 45.1% adhered to guidelines in primary care, in the Cape Town Metro district, South Africa, while the reasons of non-adherence included undocumented indication, wrong choice of medicine, incorrect treatment duration, incorrect dose and antibiotic prescribed, when not indicated (Gasson et al., 2018).

Of all the antibiotics prescribed for inpatients in this current study, 33.33% were prescribed by generic names, which is much lower than the optimal value of 100%, while 100% were prescribe from the EML (only 1 facility had 95% from the EML). Most patients were on injectable antibiotics throughout their admission period, which indicates that a change from intravenous to oral dosage was not implemented. According to Mendelson (2015), a change of administration route, from intravenous to oral, is the corner stone of the Antimicrobial Stewardship Programme (ASP). This suggests a need for the establishment and implementation of ASP at facility level, to monitor the antimicrobial usage, by performing a Medicine Utilization Evaluation (MUE), to audit rational use and provide feedback.

5.5. Limitations

One limitation in this current study was the total number of folders assessed for the antimicrobial use indicators was limited, because of only one data collector (the researcher), time constraints, as well as the distance travelled to the various facilities. Secondly, for facility indicators, the physical evidence of the existence of Pharmacy and Therapeutic Committee [PTC], Standard Treatment Guidelines [STG] or formulary, Surgical Prophylaxis Protocol, and Infection Control Guidelines, were not confirmed; however, the researcher assumed that the pharmacists were honest during the interviews.

CHAPTER SIX

CONCLUSION & RECOMMENDATIONS

6.1. Introduction

The rational use of medicine is a worldwide concern, and a current topic of interest. For reason provided in this current study, it is important to promote the rational use of medicine. Many developing countries still experience challenges with the access to essential medicines, while those who have improved access to essential medicines, experience challenges with the rational usage of medicines (Ojo et al., 2014). When medicines, such as antimicrobials, are irrationally used, resistance to the medicines results (Gasson et al., 2018). Additionally, pharmaceutical companies are not developing new antimicrobials; therefore, the treatment of common infectious diseases is becoming more difficult and expensive (Junaid et al., 2018). The South Africa National Department of Health [NDoH] is introducing the National Health Insurance (NHI) initiative, to improve access to medical services, including access to essential medicines, which necessitates strategies to promote more rational use of medicine, supervision, and maintenance of effective utilization of the NHI (MSH, 2012).

6.2. Conclusions

The researcher draws the following conclusions from the findings of this study. Firstly, the irrational use of medicine is still a challenge, with polypharmacy being one of the leading causes. Additionally, at medical schools, the generic names of medicines are taught to students, while reference books and clinical guidelines also use generic names; however, prescribers still find it difficult to prescribe medicines, by using their generic names. The polypharmacy has been identified as medicine use problem which may result in adverse drug reaction, poor adherence to treatment and subsequently increased cost to both community and healthcare facilities. Common infectious diseases, such as pneumonia, are still not managed in accordance with standard treatment guidelines, which might be due to poor monitoring, and enforcement of adherence to guidelines, either local, or international, and this indicate inadequate patient care. Finally, there is a potentially huge problem with the prolonged duration of intravenous antimicrobials. The research objectives to identify and describe medicine use problem, use of antimicrobial as baseline, and quality of patient care has been accomplish.

6.3. Recommendations

The findings of this current study has revealed that there is a possibility that medicines are used irrationally, with polypharmacy being one of the main influencing factors. Therefore, the researcher recommends that, the provincial and facilities' Pharmacy and Therapeutic Committee (PTC) be re-engineered, and healthcare providers educated regarding the importance of the PTC, as well as its objectives. In addition, the functioning of the PTCs need to be monitored, all the facilities involved in this current study, reported that their PTC met on a monthly basis; however, they did not achieve their objectives, for example, medicine selection for a hospital formulary, as well as continuous evaluation of medicine utilisation. Besides the re-engineering of the PTCs, it is recommended that Pharmacovigilance, as well as antimicrobial stewardship programmes be established at facility level, and healthcare professionals trained to perform a medicine utilization review (elaborated below)

The establishment of a PTC is one of the 12 interventions advocated by the WHO to promote RMU (MSH, 2012). The South African NDP also advocates for the establishment and implementation of a PTC in the public and private sector, as a functional PTC is the cornerstone of the NDP (RSA, NDoH, 2015). Scant research exists on the impact of PTC intervention, in promoting more RMU (Laing et al., 2001); therefore, there is still a need to strengthen the role of provincial, district and facility PTCs.

Most studies suggest that educational strategies are more effective, when conducted frequently, instead of a one-off (WHO, 2001). According to the findings of this current study, the PTC training was conducted between January 2007 and July 2011, across all provinces. The WHO (2006) advocates the inclusion of RMU education in the undergraduate curriculum for nurses, doctors and pharmacist. However, current PTC members are mostly senior healthcare professionals, who had not received the training during their undergraduate and professional development; therefore, if the current PTC members are not re-trained on the role and functions of a PTC, the future graduates, who may have had RMU training during their undergraduate studies, may adopt the current PTC practice.

Healthcare workers receive limited basic training, or continuous education on medicine use; therefore, they require training and mentorship, to improve their knowledge regarding PTCs (SIAPS, 2012). It is recommended that PTCs be trained and supervised, to ensure that they are able to perform their core functions, which include, formulary development and management, implementation of national policies and procedures, RMU analysis and intervention, as well as procurement and improve availability of essential medicines.

The South African National guidelines indicate that, in order for PTCs to promote more RMU, the committee must be able to identify medicine use problems. This would be achieve when the PTC members are able to perform Anatomical Therapeutic Chemical Classification (ATC), DDD, ABC analysis, VEN analysis, and individual level studies (WHO/INRUD core drug use indicators), as well as the MUE, implying that, with all these findings, they should be able to develop strategies to improve medicine use. The PTCs must be encouraged to attend conferences and seminars (RSA, NDoH, 2019). The PTC is the cornerstone of the NDP; therefore, it could be argued that it would be a multidisciplinary forum, which the NHI could rely on.

Polypharmacy is one example of irrational medicine use that needs to be examined, urgently, to prevent potential ADRs, which affect therapeutic outcomes, complications, and patients' wellbeing (Alomar, 2014). Research has established that the more medication (in number) patients use, the higher their risk of developing ADRs; however, this does not necessarily imply that patients should not take more than one medication (Salwe et al., 2016). Elderly patients are the most frequent users of health services and medicines (Spinewine, 2005); however, unfortunately, due to aging, they are the individuals, who are at high risk of developing ADR. Elderly patients, commonly, suffer from more than one disease, or attend more clinics on the same day; consequently, they receive more medication, and often have difficulty remembering their medication regimen (Spinewine et al., 2005). Steyn et al. (2008) observed that more than 30% of hypertension and diabetic patients did not take their medications on the consultation day, resulting in elevated vitals, with prescribers adding more medicines, or increasing dosages.

It is recommended that, when investigating polypharmacy, the focus should not be on the negative economic impact, only, but more on the patient's safety. Reportedly, only a few ADRs are reported worldwide. The prescribing cascade, caused by polypharmacy, where certain medicines are prescribed to treat adverse effects caused by other medications, results in an endless cycle of medications used by patients (Alomar, 2014). To prevent this prescribing cascade, spontaneous reporting is vital, while training and mentorship on reporting, need to be more frequent.

Healthcare providers need to be encouraged to be stewards of antimicrobial use. The researcher recommends urgent development and implementation of a multidisciplinary ASPs at facility level.

The antimicrobial stewardship team must be able to develop and implement treatment protocols, enforce adherence to treatment protocols by prescribers, control and regulate all aspects of antimicrobial use, including prescribing, dispensing and administration (Mendelson, 2015). According to Hogan et al. (2016), an ASP is a required organizational practice, for the accreditation of hospitals in Canada. In this current study, a multidisciplinary community stewardship approach has indicated an improvement in antibiotic prescribing in weekly ward rounds, where antibiotic prescriptions decreased by 19.6%, without an increase of inpatients' mortality, or a 30 day readmission rate (Mendelson, 2015). The two interventions that effected a reduction in antibiotic prescription, were restrictive intervention, as the prescribing habits of prescribers were micro-managed, and persuasive intervention, in which audits and feedback were conducted (Mendelson, 2015). Finally the committee must have a committed leadership, and be able to promote regular training and education on antibiotic stewardship, as well as a dedicated weekly time allocation, to encourage staff to participate in antibiotic stewardship ward rounds (Junaid et al., 2018).

6.4. Recommendations for future research

The researcher recommends the need to research the benefit of collecting culture sensitivity on admission, against delayed culture sensitivity tests, as a clinical perspective, versus a financial perspective. Additionally, the impact of the PTC's availability, in promoting the rational use of medicine, needs to be explored. Whether a full-time ward pharmacist would improve the rational use of medicine, and maintain the balance, should also be investigated. The rational use of metronidazole infusion with inpatients requires some serious scrutiny. Finally, the researcher also recommends that future research be conducted on the impact of the Pharmacovigilance programme on healthcare, as well as the societal perspective.

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ANNEXURES

Annexure A: Prescribing indicators tool

UNIVERSITY OF THE WESTERN CAPE
Private Bag X 17, Bellville 7535, South Africa

Prescribing indicators

Name of unit______________________________Collector:____________________

_________________Date:_____________

	Folder number	Date of prescription	Age (years)	Gender (F/M)	No. of medicine prescribed	Number of medicines prescribed in INN/Generic	Antimicrobial prescribed (YES/NO)	Injection prescribed (YES/NO)	Number of medicines prescribed from EML	Primary Diagnosis
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
					Average:	Percentage (%):	Percentage (%):	Percentage (%):	Percentage (%):	Average:

Annexure B: Facility indicators tool

UNIVERSITY OF THE WESTERN CAPE
Private Bag X 17, Bellville 7535, South Africa

Facility indicators

Name of facility: ___________________________Collector:____________________

_________________Date:____________

Does hospital have PTC?	
If affirmative, when was the last meeting?	
Does the hospital have a formulary list or EML authorized for acquisition of medicine by the hospital?	
Date of the last revision of the formulary list or EML?	
How many antimicrobials are on the formulary list or EML?	
Are all of the medicine in formulary identified by generic names?	
Are the formulary or EML medicines based on those recommended in STG?	
Does the hospital have STG for infectious disease for most prevalent conditions?	
Pneumonia?	
Date of last revision for STG for infectious disease?	
Does hospital have protocols or norms for surgical prophylaxis with antimicrobials?	
Does hospital have infection control guidelines?	

Annexure C: Record of antimicrobial treatment tool

UNIVERSITY OF THE WESTERN CAPE
Private Bag X 17, Bellville 7535, South Africa

Record of antimicrobial treatment

Name of unit______________________________**Collector:**____________________

_________________**Date:**____________

Patient information							Prescribing indicators							
Folder Number	Pneumonia case (YES/NO)	Age (years)	Gender (F/M)	Was antimicrobial prescribed (YES/NO)	Number of days in hospital	Was sensitivity test done (YES/NO)	Name(s) of antimicrobial(s) prescribed	Prescribed by generic name (YES/NO)	Antimicrobial on EML (YES/NO)	Dosage form and strength	Dosage frequency per day	Total days of treatment prescribed	Number of doses actually administered
Total cases													

Annexure D: University of Western Cape - Ethics Approval

UNIVERSITY *of the* WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 4111/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

08 June 2018

Dr R Coetzee
School of Pharmacy
Faculty of Natural Science

Ethics Reference Number: BM18/4/5

Project Title: Evaluation of rational use of medicines in public healthcare facilities

Approval Period: 07 June 2018 – 07 June 2019

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE

Annexure E: Limpopo Province Department of Health - Ethics Approval

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Enquiries: Stander SS (015 293 6650) Ref: **LP_2018_06_008**

R Coetzee , V Valoyi
University of Western Cape

Greetings,

RE: Evaluation of rational use of medicines in public healthcare facilities

The above matter refers.

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
   - In the course of your study there should be no action that disrupts the services, or incur any cost on the Department.
   - After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 3 year period.
   - If the proposal has been amended, a new approval should be sought from the Department of Health.
   - Kindly note, that the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated.

[signature]
Head of Department

06/08/2018
Date

Private Bag X9302 Polokwane
Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.
Website: http/www.limpopo.gov.za

The heartland of Southern Africa – Development is about people!

Annexure F: Project Information & Informed Consent

UNIVERSITY OF THE WESTERN CAPE

Private Bag X 17, Bellville 7535, South Africa

PROJECT INFORMATION & INFORMED CONSENT
HEALTHCARE WORKER

Dear Participant,

Thank you for your willingness to listen to me. I am a postgraduate student from the School of Pharmacy at the University of the Western Cape. I am doing research on the use of medicines in public health facilities. If you have any questions please do not hesitate to ask me or use the contact details at the end of this letter.

Project Title: Evaluation of rational medicine use in public healthcare facilities.

Special Instructions:
This information and consent form may contain words that are new to you. If you read any words that are not clear to you, please ask the person who gave you this form to explain them to you.

Purpose:
You are being asked to take part in a research project evaluating rational use of medicines in public healthcare facilities. You have been invited to participate because we would like to measure the performance of health care providers in relating to appropriate use of medicines, availability of adequate supply of medicines and understand patients experience at health facilities and how well are they prepared to take medicines prescribed and dispensed to them. The purpose of this research project is to learn how medicines are used by health providers and patients, and what kind of strategies can be used to improve their rational use.

Procedures:
If you agree to take part in this research study, you will be asked a series of questions about rational prescribing practices, e.g. availability of an essential medicine list, availability of standard treatment guidelines, existence of committees that evaluate medicine use, etc. The session will last for 15-30 minutes.

Risks/Discomforts:
There is no anticipated discomfort for those contributing to this study, so risk to participants is minimal.

Benefits:
Although you may not directly benefit from taking part in this study, your participation in this project may help understand current use of medicine and develop strategies to promote rational medicine use. Patients and healthcare providers may learn about possible resources.

Confidentiality:
Your confidentiality will be guaranteed. You will be identified by a code which will be linked to the data sets gathered from surveying you but not your name. The data collector will not ask you for your name. The informed consent form you will sign or thumbprint will be kept in a locked cupboard free from any other person. Data will also be stored on a computer and password protected and only accessible to the researcher. After the research is the manual data sheets will be destroyed without leaving a trace.

Voluntary Participation/Withdrawal:
Your decision to take part in this research project is entirely voluntary. You may refuse to take part or you may withdraw from the project at any time without penalty.

What if you have questions?
This research is being conducted by Mr Vutomi Valoyi at the University of the Western Cape. If you have any questions about the research study itself, please contact him.

Mr Valoyi V.F
Botlokwa Hospital
Private Bag X544, Dwars River 0812
Limpopo Province
Tel: +27 (0)15 527 8097
Email: vfvaloyi@gmail.com

Should you have any questions regarding this study and your rights as a research participant or if you wish to report any problems you have experienced related to the study, please contact the supervisor, Dr Renier Coetzee.

Dr. Renier Coetzee
School of Pharmacy
University of the Western Cape
Private Bag X17, Bellville 7535
Tel: +27 (0)21 959 3665
Email: recoetzee@uwc.ac.za

Alternatively you can contact the Director of the School of Pharmacy, Professor Sarel Malan.

Prof Sarel Malan
School of Pharmacy
University of the Western Cape
Private Bag X17, Bellville 7535
Tel: +27 (0)21 959 3190
Email: sfmalan@uwc.ac.za

The Biomedical Research Ethics Committee (BMREC) provided approval to conduct the study. The approval number (*to be inserted upon receiving the number*).

Biomedical Research Ethics Committee (BMREC)
Research Development
Room 28 C Block New Arts Building
University of the Western Cape, Robert Sobukwe Road
Bellville, 7535
Tel: +2721 9592988
Email: research-ethics@uwc.ac.za

Annexure G: Facility indicators questionnaire per facility

UNIVERSITY OF THE WESTERN CAPE

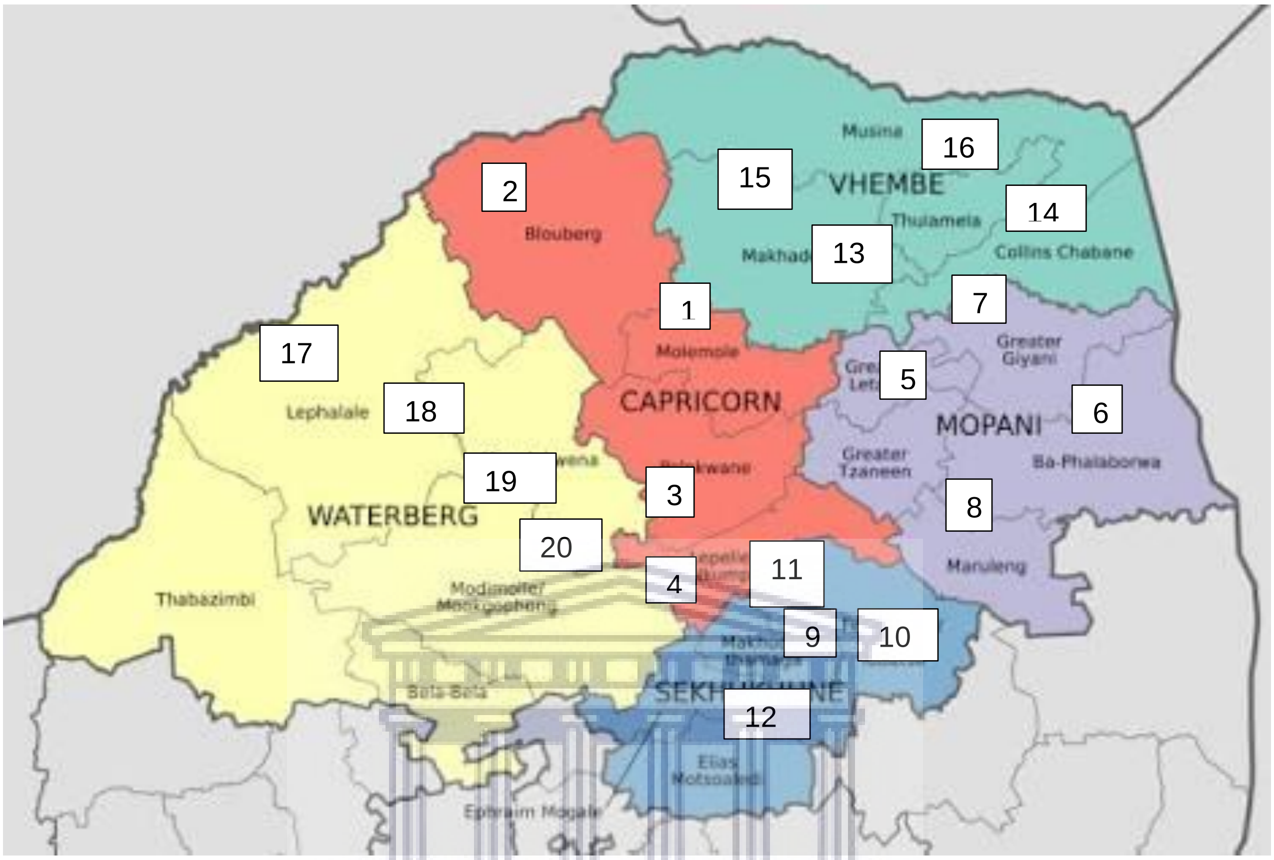
Private Bag X 17, Bellville 7535, South Africa

Record of Facility indicator

FACILITIES																				
QUESTIONAIRE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Does hospital have PTC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Last meeting	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Availability of formulary or EML	N	N	Y	Y	P	P	Y	Y	Y	Y	Y	P	N	Y	Y	P	Y	Y	P	Y
Last revision of formulary or EML (Years)			4	4	1	1	5	6	5	5	4	1		<1	5	1	5	4	1	5
Are all medicine in generic name			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y
Availability of STG for infectious diseases	Y	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y
Last revision of STG for infectious disease (Years)	4		4	6	2			6	5		4	1		<1	5	1	5		4	5
Availability of protocol for surgical prophylaxis with antimicrobial	N	N	Y	Y	Y	Y	N	N	N	N	N	Y	Y	N	Y	Y	N	N	Y	Y
Availability of infection control guidelines	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y- Yes, N- No, M- Monthly, P- Provincial

Annexure H: Distribution of Hospitals included in this study



Annexure I: Antimicrobial use indicator (Pneumonia cases)

UNIVERSITY OF THE WESTERN CAPE
Private Bag X 17, Bellville 7535, South Africa

Record of antimicrobial treatment (Pneumonia cases)

Pneumonia case	Age (years)	Gender	Antimicrobial prescribed	Hospital stay	Culture collected	Number of antimicrobial prescribed	Names of antimicrobial prescribed	Prescribed according	Generic name	On EML	Strength and route	Frequency
YES	1	F	yes	3	NO	2	ROCEPHIN, AMOXYL	YES	0	2	125MG IV, 250MG P.O	12HRLY, 8HRLY
YES	1	F	yes	5	NO	4	AMPICILLIN, GENTAMYCIN, BACTRIM, AMOXYL	YES	2	4	275MG IV, 275MG IV, 5ML P.O, 7ML P.O	6HRLY, 24HRLY, 24HRLYY, 8HRLY
YES	4	M	yes	2	NO	2	AMPICILLIN, AMOXYL	YES	1	2	400MG IV, 7.5ML	6HRLY, 8HRLY
YES	51	F	yes	2	NO	1	AUGMENTIN	YES	0	1	1.2G IV	8 HRLY
YES	1	M	yes	2	NO	3	AMPICILLIN, GENTAMYCIN, CHLORAMEX	YES	2	3	140MG IV, 160MG IV	8HRLY 24 HRLY
YES	1	F	yes	3	NO	2	GENTAMYCIN, AMPICILLIN	YES	2	2	57MG IV, 40MG IV	24 HRLY 6 HRLY
YES	1	M	yes	4	NO	3	GENTAMYCIN, AMPICILLIN, AMOXYL	NO	2	3	400MG IV, 300MG IV, 250MG P.O	24HRLY 6 HRLY 8 HRLY
YES	4	M	yes	7	NO	3	AMPICILLIN, GENTAMYCIN, AMOXYL	YES	2	3	600MG IV, 60MG IV, 600MG P.O	6HRLY, 24HRLY 8 HRLY
YES	2	F	yes	6	NO	3	AMPICILLIN, GENTAMYCIN, AMOXYL	YES	2	3	225MG IV, 45MG IV, 225MG P.O	6HRLY, 24HRLY, 6HRLY
YES	1	F	yes	2	NO	1	AMOXIL	YES	0	1	500MG P.O	12HRLY
YES	2	M	yes	2	NO	2	AMPICILLIN, AUGMENTIN	NO	1	2	300MG IV, 125MG P.O	8HRLY 8 HRLY

YES	33	F	yes	5	NO	4	AMPICILLIN, FLAGYL, AMOXYL, BACTRIM	NO	0	4	1G IV, 500MG IV,500MG P.O, 960MG P.O	8HRLY, 8HRLY, 8HRLY, 24HRLY
YES	1	F	yes	2	NO	2	AMPICILLIN, AMOXIL	YES	1	2	102MG IV, 250MG P.O	6HRLY, 8HRLY
YES	1	F	yes	2	NO	2	AMPICILLIN, AUGMENTIN	YES	1	2	350MG IV, 2.5ML P.O	6HRLY, 8HRLY
YES	2	F	yes	3	NO	2	ROCEPHIN, AUGMENTIN	NO	0	2	325MG IV, 250MG P.O	8HRLY, 8HRLY
YES	53	M	yes	2	NO	2	AUGMENTIN, BACTRIM	YES	0	2	1.2G IV, 960MG P.O	12HRLY 24 HRLY
YES	47	M	yes	6	NO	2	ROCEPHIN, FLAGYL	NO	0	2	1G IG, 500MG IV	12HRLY, 8HRLY
YES	7	M	yes	3	NO	2	ROCEPHIN, AUGMENTIN	YES	0	2	400MG IV, 250MG P.O	12HRLY, 8HRLY
YES	33	F	yes	8	NO	1	AUGMENTIN	YES	0	1	1.2G IV	8HRLY
YES	1	M	yes	5	NO	4	AMPICILLIN GENTAMYCIN ROCEPHIN AUGMENTIN	YES	2	4	350 MG IV 35MG IV 250MG IV 125MG P.O	6 HRLY 24 HRLY 12 HRLY 8 HRLY
YES	4	F	yes	3	NO	2	ROCEPHIN AMOXYL	YES	0	2	500MG IV 250MG P.O	12 HRLY 8 HRLY
YES	33	M	yes	10	NO	1	AUGMENTIN	YES	0	1	1.2G IV	8 HRLY
YES	7	M	yes	2	NO	2	AUGMENTIN AMOXYL	YES	0	2	300MG IV 125MG P.O	8 HRLY 8HRLY
YES	33	M	yes	16	NO	2	ROCEPHIN PEN VK	YES	1	2	1G IV 500MG P.O	12 HRLY 12 HRLY
YES	32	M	yes	6	NO	2	AMPICILLIN AUGMENTIN	YES	1	2	1G IV 625MG P.O	6 HRLY 12 HRLY
YES	1	F	yes	5	NO	2	AMPICILLIN AMOXYL	YES	1	2	240MG IV 125MG P.O	6 HRLY 8 HRLY
YES	3	F	yes	2	NO	3	AMPICILLIN GENTAMYCIN AMOXYL	NO	2	3	320MG IV 70MG IV 125MG P.O	8 HRLY 24 HRLY 8 HRLY

YES	63	F	yes	5	NO	1	AUGMENTIN	YES	0	1	1.2G IV 625MG P.O	8 HRLY 8HRLY
YES	21	F	yes	11	YES	3	AMPICILLIN FLAGYL AUGMENTIN	NO	1	3	500MG IV 500MG IV 1.2G IV	6 HRLY 8 HRLY 8 HRLY
YES	73	M	yes	3	NO	1	AUGMENTIN	YES	0	1	600MG IV	6 HRLY
YES	1	F	yes	5	NO	2	AMPICILLIN AMOXYL	YES	1	2	240MG IV 125MG P.O	6 HRLY 8 HRLY
YES	60	M	yes	10	NO	2	ROCEPHIN AZITHROMYCIN	YES	1	2	1G IV 500MG P.O	12 HRLY 24 HRLY
YES	84	M	yes	15	NO	2	FLAGYL ROCEPHIN	NO	0	2	500MG IV 1G IV	8 HRLY 12 HRLY
YES	4	M	yes	3	NO	3	AMPICILLIN GENTAMYCIN AUGMENTIN	YES	2	3	500MG IV 90MG IV 125MG P.O	6 HRLY 24 HRLY 8 HRLY
YES	43	M	yes	7	NO	2	AMPICILLIN AUGMENTIN	YES	1	2	500MG IV 625MG P.O	6 HRLY 8HRLY
YES	44	M	yes	5	YES	3	AMPICILLIN AZITHROMYCIN AMOXYL	YES	2	3	1G IV 500MG P.O 500MG P.O	6 HRLY 24 HRYL 8 HRLY
YES	55	F	yes	3	NO	3	AMPICILLIN AZIITHROMYCIN AUGMENTING	YES	2	3	1G IV 500MG P.O 1G P.O	6 HRLY 24 HRLY 8 HRLY
YES	18	F	yes	2	YES	3	AMPICILLIN AZITHROMYCIN AUGMENTIN	YES	2	3	1G IV 500MG P.O 1G P.O	6 HRLY 24 HRLY 8 HRLY
YES	39	F	yes	5	NO	4	ROCEPHIN FLAGYL AUGMENTIN AZITHROMYCIN	NO	1	4	1G IV 500MG IV 1G P.O 500MG P.O	12 HRLY 8 HRLY 8 HRLY 24 HRLY
YES	51	F	yes	6	NO	3	ROCEPHIN AUGMENTIN AZITHROMYCIN	NO	1	3	1G IV 1.2G IV 500MG IV	12 HRLY 8 HRLY 24 HRLY
YES	68	M	yes	23	NO	5	ROCEPHIN AUGMENTIN CIPROBAY FLAGYL AMOXYL	NO	0	5	1G IV 1.2G IV 250MG P.O 400MG P.O 500MG P.O	12 HRLY 8 HRLY 12 HRLY 8 HRLY 8 HRLY
YES	1	M	yes	2	NO	2	AMPICILLIN AMOXYL	NO	1	2	120MG IV 125MG P.O	8 HRLY 8HRLY

YES	1	M	yes	5	NO	3	AMPICILLIN GENTAMYCIN AMOXYL	YES	2	3	450MG IV 54MG IV 125MG P.O	6 HRLY 24 HRLY 8 HRLY
YES	1	F	yes	8	NO	2	AMPICILLIN GENTAMYCIN	YES	2	2	250MG IV 40MG IV	6 HRLY 24 HRLY
YES	1	F	yes	6	YES	1	ROCEPHIN	YES	0	1	132MG IV	12 HRLY
YES	53	F	yes	2	NO	1	AZITHROMYCIN	YES	1	1	500MG P.O	24 HRLY
YES	23	F	yes	8	NO	1	AUGMENTIN	YES	0	1	1.G IV	12 HRLY
YES	42	F	yes	5	NO	1	AUGMENTIN	YES	0	1	1.2G IV	8 HRLY
YES	58	F	yes	7	NO	2	AUGMENTIN ROCEPHIN	YES	0	2	1.2G IV 2G IV	8 HRLY 12 HRLY
YES	43	F	yes	10	YES	1	AUGMENTIN	YES	0	1	1.2G IV 625MG P.O	8 HRLY 8HRLY
YES	28	F	yes	14	NO	3	FLAGYL ROCEPHIN AUGMENTIN	NO	0	3	500MG IV 1G IV 1.2G IV 375MG P.O	8 HRLY 12 HRLY 8 HRLY 8 HRLY
YES	3	M	yes	13	YES	2	ROCEPHIN AZITHROMYCIN	YES	1	2	1G IV 500MG P.O	12 HRLY 24 HRLY
YES	58	M	yes	9	NO	1	ROCEPHIN	YES	0	1	1G IV	12 HRLY
YES	29	M	yes	15	NO	2	ROCEPHIN FLAGYL	NO	0	2	2G IV 500MG IV	12 HRLY 8 HRLY
YES	58	M	yes	14	NO	2	AMPICILLIN FLAGYL	YES	1	2	500MG IV 500MG IV	6 HRLY 8 HRLY
YES	58	M	yes	23	YES	4	ROCEPHIN CIPROBAY AMPICILLIN FLAGYL	NO	1	4	1G IV 500MG P.O 1G IV 400MG P.O	12 HRLY 12 HRLY 6 HRLY 8 HRLY
YES	1	F	yes	5	NO	3	AMPICILLIN AUGMENTIN ROCEPHIN	NO	1	3	300MG IV 125MG P.O 250MG IV	8 HRLY 8 HRLY 24 HRLY
YES	1	F	yes	3	NO	3	AMPICILLIN FLAGYL AUGMENTIN	NO	1	3	250MG IV 5ML P.O 125MG P.O	8 HRLY 8 HRLY 8 HRLY
YES	4	F	yes	2	NO	3	AMPICILLIN GENTAMYCIN AMOXICILLIN	NO	3	3	500MG IV 70MG IV 250MG P.O	12 HRLY 24 HRLY 8 HRLY
YES	5	M	yes	1	NO	5	ROCEPHIN AMPICILLIN GENTAMYCIN BENZYL-ENICILLIN AUGMENTIN	NO	3	5	250MG IV 600MG IV 95MG IV 6000Iu IM 375MG P.O	STAT 12 HRLY 24 HRLY STAT 8 HRLY

YES	3	M	yes	5	NO	3	AMPICILLIN GENTAMYCIN AMOXICILLIN		3	3	250MG IV 100MG IV 250MG	8 HRLY 12 HRLY 24 HRLY 8 HRLY
YES	40	F	yes	5	YES	3	AMPICILLIN AZITHROMYCIN AMOXYL	YES	2	3	1G IV 500MG P.O 500MG P.O	6 HRLY 24 HRLY 8 HRLY
YES	48	M	yes	3	NO	3	AMPICILLIN AZITHROMYCIN AUGMENTIN	YES	2	3	1G IV 500MG P.O 1G P.O	6 HRLY 24 HRLY 8HRLY
YES	23	F	yes	2	YES	2	AMPICILLIN AZITHROMYCIN	YES	2	2	1G IV 500MG P.O	6 HRLY 24 HRLY
YES	35	M	yes	5	NO	4	ROCEPHIN FLAGYL AUGMENTIN AZITHROMYCIN	NO	1	4	1G IV 500MG IV 1G P.O 500MG P.O	12 HRLY 8 HRLY 8 HRLY 24 HRLY
YES	47	M	yes	6	NO	3	ROCEPHIN AUGMENTIN AZITHROMYCIN	NO	1	3	1G IV 1.2G IV 500MG P.O	12 HRLY 8 HRLY 24 HRLY

Annexure J: Editorial Certificate

Idea Corporation t/a
AQUARIAN PUBLICATIONS

14 July 2020

To whom it may concern

Dear Sir/Madam

RE: Editorial certificate

This letter serves to prove that the thesis listed below was language edited for proper English, grammar, punctuation, spelling, as well as overall layout and style by myself, publisher/proprietor of Aquarian Publications, a native English speaking editor.

Thesis title

EVALUATION OF RATIONAL USE OF MEDICINES IN PUBLIC HEALTHCARE FACILITIES

Author

Vutomi Valoyi

The research content, or the author's intentions, were not altered in any way during the editing process, and the author has the authority to accept, or reject my suggestions and changes.

Should you have any questions or concerns about this edited document, I can be contacted at the listed telephone and fax numbers or e-mail addresses.

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