UNIVERSITY OF KWAZULU-NATAL ™

INYUVESI YAKWAZULU-NATALI

PRESCRIPTION PATTERN MONITORING OF OUTPATIENT PEDIATRIC PATIENTS

BY

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Submitted in fulfilment of the requirements for the degree of Master of Pharmacy in the Discipline of Pharmaceuticals Sciences, School of Health Sciences in the College of Health Sciences, University of KwaZulu-Natal.

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PREFACE

This dissertation is presented in a manuscript format in accordance with the College of Health Sciences guidelines for thesis/dissertation submissions at the University of KwaZulu-Natal. The findings of the study are presented as two manuscripts in chapters 3 and 4 of this dissertation. One manuscript has been submitted for publication to the *International Journal of Pediatrics and Adolescent Medicine (IJPAM)* and another manuscript was submitted to the *African Journal of Primary Health Care & Family Medicine (PHCFM)*. The references used in the manuscripts were cited according to the instructions/guidelines for authors as required by the journals. A complete reference list is presented at the end of each manuscript chapter, in accordance with the reference style of the journals.

The dissertation consists of five chapters as follows:

- Chapter 1: Introduction highlights the background, problem statement and rationale of the study. It further describes the research questions, the aim and objectives of the study, a brief methodology and overview of the dissertation.

- Chapter 2: Literature review provides a review of literatures on irrational prescribing in paediatrics and its consequences, various approaches to curb irrational drug use namely prescription monitoring, clinical guidelines such as standard treatment guidelines and essential medicine list, the World Health Organization prescribing indicators, institutional guidelines and pharmaceutical therapeutic committees.

- Chapter 3: Manuscript 1 for publication presents an original manuscript article titled "Prescribing patterns in paediatrics outpatient department at a tertiary care public sector hospital in KwaZulu-Natal, South Africa" which was submitted according to IJPAM guidelines.

- Chapter 4: Manuscript 2 for publication presents an original manuscript article titled "Compliance with standard treatment guidelines and essential medicine list in paediatric outpatients at a tertiary care public sector hospital in KwaZulu-Natal, South Africa" which was submitted according to PHCFM guidelines.

- Chapter 5: Provides the synthesis which includes general conclusions, significant findings, strengths and limitations of the study and recommendations are provided.

DECLARATION 1: DISSERTATION SUBMISSION

This is to certify that the contents of this dissertation are the original work of:

Student: Zerisenay Tsegay (216076821)

Signed: _____

Date: _____

As the student's supervisor/co-supervisor, we have approved this dissertation for submission.

Supervisor: Dr Frasia Oosthuizen

Signed: _____

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Co-Supervisor: Dr Elizabeth Ojewole

Signed: _____

Date: _____

DECLARATION 2 - PLAGIARISM

I, Zerisenay Tsegay, declare that:

1. The research reported in this dissertation, except where otherwise indicated, is my original work.

2. The work described in this dissertation has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

3. This dissertation does not contain other persons writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:

a) Their words have been re-written but the general information attributed to them has been referenced.
b) Where the exact words of other people have been used, their writing has been placed inside quotations, and referenced.

4. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the reference sections.

Signed _____ Date _____

DECLARATION 3 – ETHICS APPROVAL AND GATE KEEPER PERMISSION

1. Ethical approval was obtained from the Biomedical Research Ethics Committee, University of KwaZulu-Natal (BREC Ref: BE492/17). A copy of the approval is attached as Annexure 1.

2. This study was registered on the South African National Health Research Database (NHRD) (Ref: KZ_201710_023) and approved by Health Research and Knowledge Management (HRKM Ref: 422/17). A copy of the registration/approval letter is attached as Annexure 2.

3. Gate keeper permission to access patient files was obtained from the KwaZulu-Natal Department of Health and King Edward VIII hospital administration (Ref: KE 2/7/1 46/2017). A copy of this permission letter has been attached as Annexure 3.

DECLARATION 4 – MANUSCRIPTS FOR PUBLICATION

1. Zerisenay Tsegay, Elizabeth Ojewole, Wilbert Sibanda, Frasia Oosthuizen. Prescribing Patterns in an Outpatient Paediatrics Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa. *Submitted manuscript (IJPAM_2019_65). The manuscript was drafted using the data generated in this study and submitted to the International Journal of Pediatrics and Adolescent Medicine, an international Scopus journal. The manuscript is currently under review and the cover page is attached as Annexure 4, the confirmation letter is attached as Annexure 5.*

*Z*erisenay Tsegay designed the research project, performed all literature searches, collected the data, and performed statistical analysis and interpreted results. Dr F Oosthuizen and Dr E Ojewole (as the Supervisor/Co-supervisor) as well as Dr W Sibanda (the Statistician) directed the research and contributed to the overall project design, data analysis and interpretation and writing of the manuscripts for journal submission. All the authors prepared, reviewed and finalized the manuscripts for journal submission.

2. Zerisenay Tsegay, Frasia Oosthuizen, Wilbert Sibanda, Elizabeth Ojewole. Compliance with Standard Treatment Guidelines and Essential Medicine List in Paediatric Outpatients at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa. *Submitted manuscript – PHCFM 2097. The manuscript was drafted using the data generated in this study and submitted to the African Journal of Primary Health Care & Family Medicine, a ScieLO SA journal. The manuscript is currently under review and the submission confirmation letter and the status are attached as Annexure 6.*

Zerisenay Tsegay designed the research project, performed all literature searches, collected the data, and performed statistical analysis and interpreted results. Dr F Oosthuizen and Dr E Ojewole (as the Supervisor/Co-supervisor) as well as Dr W Sibanda (the Statistician) directed the research and contributed to the overall project design, data analysis and interpretation and writing of the manuscripts for journal submission. All the authors prepared, reviewed and finalized the manuscripts for journal submission.

DEDICATION

This work is dedicated to the Almighty God, who gave me courage and strength to carry on with my studies, my father Beyene Tsegay for his continuous support and encouragement throughout, my mother Almaz Tesfamariam who always consoled me when my spirits were low. I will always appreciate all that you have done.

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Thanks to the management of the hospital for granting me permission to conduct the study, the pharmacy staff for their kind cooperation and the staffs of the medical record office for their assistance during data collection.

And lastly, my gratitude goes to the University of KwaZulu-Natal, College of Health Sciences (CHS) for funding this study.

LIST OF ABBREVIATIONS /ACRONYMS

ADR	Adverse drug reactions
BPCA	Best Pharmaceuticals for Children Act
CI	Confidence Interval
CTM®	Chlortrimeton
DOH	Department of Health
EML	Essential medicine list
EMA	European Medicines Agency
FDA	Food and Drug Administration
GASI	Gastric Acid Secretion Inhibitor
INRUD	International Network for the Rational Use of Drugs
INN	International non-proprietary name
IQR	Interquartile range
ME	Medication error
NBD	National Burden of Disease
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NDP	National Drug Policy
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds Ratio
PREA	Pediatric Research Equity Act
PTCs	Pharmaceutical and therapeutics committees
PPMS	Prescription pattern monitoring studies
SD	Standard deviation
STGs	Standard treatment guidelines
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
WHO	World Health Organization

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ABSTRACT

Background and Aim

Prescribing for paediatric patients can be challenging for prescribers as children are especially vulnerable to harmful effects of drugs due to differences in pharmacokinetics and pharmacodynamics as well as the limited availability of licensed drugs in their appropriate dosage forms. The World Health Organisation has estimated that over 50% of drugs globally are prescribed inappropriately. Prescription pattern monitoring studies (PPMS) are tools for assessing the prescribing, dispensing and administering of drugs. They help in explaining the extent and profile of drug use, trends, and quality of drugs and compliance of prescribing with standard treatment guidelines (STGs) and essential medicines list (EML). Regular assessment of prescribing practice and evaluation for compliance in reference with treatment guidelines is crucial in promoting rational drug use and identifying problems related to drug therapy. This study was therefore conducted to monitor the prescription patterns in paediatric outpatients and to determine the level of compliance of prescribed treatments against the South African 2017 paediatric STGs/EML at a public sector tertiary hospital located in KwaZulu-Natal, South Africa.

Methods

This was a retrospective descriptive study, based on systematic sampling of paediatric patient files visiting the outpatient department. Paediatric outpatient files containing prescriptions dated between June 1, 2016 and May 30, 2017 were used. A systematic sampling technique was used to minimize bias in the selection process and to ensure equal representation of samples. Data regarding patient demographic characteristics, diagnosis and disease condition as well as details of the treatments prescribed (drug name, dose, dosage form, frequency and duration of treatment) were extracted from patient files and captured using MS Excel® 2016. The data were analysed using the following statistical packages; the Statistical Package for Social Sciences® (SPSS®) version 25 and Minitab® version 18. Compliance was determined using the loose criteria model, a method adopted from a report by the Ministry of Health and Social Services of Namibia and the Systems for Improved Access to Pharmaceuticals and Services (SIAPS). Where applicable, associations were carried out and a p-value < 0.05 was estimated as statistically significant.

Results

A total of 327 patient files were evaluated, of which 193 (59.02%) were for male patients and 134 (40.98%) female patients. The total number of drugs prescribed was 845 constituted by 29 drug groups, of which antibiotics 155/845 (18.34%), emollients 118/845 (13.96%) and analgesics 117/845 (13.85%) were most predominantly prescribed. Of the 155 antibiotics, penicillins 55/155 (35.48%), penicillins combined with beta-lactamase inhibitors 40/155 (25.81%) and cephalosporins 39/155 (25.16%) were most commonly used. The percentage of encounters with antibiotics was 35.47% and the average number of drugs per prescription was 2.58. Out of the overall 845 drugs prescribed, 354 (41.89%) were generic drugs prescribed from the paediatric EML while 491 (58.11%) were non-generic drugs prescribed using trade names. Out of the total of 419 disease conditions assessed, 134 disease conditions were identified as most commonly diagnosed. Majority of the patients 100/134 (74.63%) did not have comorbidities, while 34/134 (25.37%) had co-occurring conditions ranging from 2 - 4 diseases. Male patients 19/34 (55.88%) presented slightly higher number of comorbidities compared to female patients 15/34 (44.12%). In order to determine compliance, disease conditions which were not listed in the 2017 paediatric STGs were excluded, resulting in 275 disease conditions. Treatments prescribed for 219/275 (79.64%) disease conditions were in accordance with the South African paediatric STGs, while treatments prescribed for 56/275 (20.36%) disease conditions did not comply with the STG recommendations.

Conclusion

There was a high level of antibiotic prescribing among the paediatric outpatients, and penicillins were the most often prescribed. The average number of drugs per prescription identified in this study was higher than that recommended by the World Health Organization. Overall, majority of the treatments prescribed conformed with the recommendations of the South African 2017 paediatric STGs, however extent of generic prescribing was low. There is a need for training of prescribers and healthcare professionals, especially regarding generic prescribing in order to promote appropriate use of drugs and overall patient safety.

CHAPTER 1
INTRODUCTION

This chapter provides a description of the background, problem statement and rationale of the study. It includes the research questions, aim and objectives of the study. A general methodology has been included to achieve the aim and objectives of the study.

1.1 Background

Drugs are important components of health care and play a vital role in the treatment, cure and prevention of different types of diseases. Rational drug use is imperative in order to achieve quality health care for patients and the community as a whole (Mahmood *et al.*, 2016). Unfortunately, irrational use of drugs remains a major problem facing most health care systems across the world (WHO, 2011). The World Health Organization (WHO) defines rational drug use as "patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community" (WHO, 2002). In simple words rational drug use is prescribing the right drug in adequate doses for a sufficient duration at the lowest cost. The concept of rational drug use dates as far back as 300 B.C, when the Greek physician Herophilus said "*medicines are nothing in themselves, but are the very hands of God if employed with reason and prudence*" (Shivhare *et al.*, 2010).

Rational drug therapy is important for all drug users, but it is of paramount importance for children. The paediatric population comprises 20-25% of the total world population, of which half live in developing countries where numerous acute and chronic diseases can affect this subpopulation (Mishra *et al.*, 2014). Children under 16 years of age form one of the largest patient groups consulting general practitioners globally, accounting for approximately 18% of medical consultations annually (Palanisamy, Loganathan and Arunachalam, 2012). Unfortunately, 50-90% of drugs currently used in children have not been studied in this population, and results obtained from clinical studies conducted in adults are often extrapolated for use in children (Yewale and Dharmapalan, 2012). Children are especially prone to harmful effects of drugs due to their under developed immunological, renal and hepatic systems, which predisposes them to various adverse drug reactions (ADRs) and drug harm (Nduka *et al.*, 2017). In addition to growth in physical size, several changes in body proportions, body composition and physiological development take place during infancy and childhood, consequently affecting their response to disease and drug therapy. This continuous development presents a challenge when formulating, prescribing and administering age appropriate treatments for children (Bracken *et al.*, 2018).

The study of prescription pattern promotes the appropriate use of drugs as it seeks to monitor, evaluate and suggest modifications in the prescribing practices so as to make medical care rational and cost-effective (Jimoh *et al.,* 2011). Prescription pattern monitoring studies (PPMS) are systematic criteria-based drug utilization studies used to assess the quality of drug therapy by evaluating data on drug prescribing, dispensing and patient use in a given health care environment against predetermined standards (WHO, 2003). PPMS play a major role in facilitating the rational use of drugs in a population by monitoring the extent and profile of drugs used, comparing the compliance of drugs used for the treatment of certain disease conditions with current treatment guidelines, determining the extent to which alternative drugs are used to treat disease conditions, assessing the extent of generic prescribing and estimating the number of patients exposed to specific drugs within a given time period at a particular setting (Jain *et al.*, 2015), (Kandula *et al.*, 2017).

Some of the key objectives of PPMS include optimizing drug therapy, preventing drug related errors, identifying specific problems associated with drug use that require further assessment and evaluation as well as ensuring prescribed treatments comply with the recommendations of current clinical guidelines such as standard treatment guidelines (STGs) and essential medicine list (EML) (Jain *et al.*, 2015). STGs are systematically developed statements comprising a list of preferred pharmaceutical and non-pharmaceutical treatments for common health problems designed to assist prescribers in making appropriate decisions for specific medical conditions (Management Sciences for Health, 2012). The WHO defines essential medicines as those that satisfy the priority health care needs of a population, that are selected with due regard to disease prevalence and public health relevance, evidence on efficacy, safety and comparative cost effectiveness of the product. Essential medicines are intended to be available at all times within the context of functioning health systems in sufficient amounts, in appropriate dosage forms, with assured quality and at a price patients and the community can afford (WHO, 2017). STGs/EML ensure rational drug therapy by maintaining consistency in treatment selection and reducing confusion among prescribers by means of providing prescribers with expert consensus on most effective and economical treatments available. STGs/EML can also serve as tools to supervise, monitor and evaluate health care practices (Gopalakrishnan, Udayshankar and Rama, 2014).

The South African STGs/EML was initially introduced in 1996 with the goal of ensuring quality health care and supply of safe, reliable and cost effective drugs to all citizens. This was subsequently followed by the implementation of STGs/EML for paediatrics in 1998 which aimed to address the specific medical needs of the subpopulation (DOH, 2017). The paediatric STGs are arranged according to the organ systems of the body and disease conditions which are described using the international disease classification system (ICD-10). Each disease condition is presented with a recommended pharmacological treatment regimen using generic drugs listed under international non-proprietary names (INN). (Perumal-Pillay and Suleman, 2016). To date, the current South African paediatric STGs/EML has been updated to its fourth edition has been implemented for mandatory use in all nine

provinces where it caters for common disease conditions that patients are treated for in health facilities (DOH, 2017).

Over the past decade, the importance of PPMS has been growing due to the vast increase in marketing of new drugs, growing concerns regarding ADRs and the increasing apprehension of drug resistance and drug cost (Gama, 2008). Currently, the evaluation of prescription pattern studies in adults and elderly patients is a highly visible topic, however similar studies focusing on paediatric patients are limited despite the widespread use of unlicensed and off-label drugs in children (Al Balushi *et al.*, 2013).

1.2 Problem statement

Irrational drug use is a major problem in health care facilities throughout the world, particularly in developing countries where health systems and mechanisms for routine drug monitoring are not well developed (Ofori-Asenso, Brhlikova and Pollock, 2016). Irrational drug use can be described as the medically inappropriate and economically ineffective use of pharmaceuticals (WHO, 2004). The WHO estimates that globally more than half of all drugs are inappropriately prescribed, dispensed or sold, and around 50% of patients fail to take their medicines correctly. Additionally, the proportion of patients in developing countries treated according to treatment guidelines in primary health care level is less than 40% and estimated to be less in tertiary health care settings (WHO, 2011). The most common problems associated with irrational drug use include, selection of drugs without consideration for cost and efficacy, over-prescribing (polypharmacy), under-prescribing, prescribing using proprietary trade names (non-generic prescribing) and failure to prescribe according to treatment guidelines (Ofori-Asenso and Agyeman, 2016).

Majority of the drugs prescribed for children have not been formally studied for safety and efficacy due to several challenges. Some of the main challenges include complex ethical concerns as children are not able to consent for themselves, high research costs compared with the potential market size, difficulty finding enough paediatric patients to participate in clinical studies and the paucity of paediatric research investigators (Turner *et al.*, 2014). These challenges have led to insufficient availability of paediatric appropriate formulations forcing health care professionals to resort to off-label prescribing and unlicensed drug use, which in turn raises issues regarding ADRs and medication errors (ME) (Khan and Ara, 2011). Paediatric patients pose a unique set of risks regarding ME, predominantly because of the need to formulate individual dosage calculations based on their weight, age and body surface area subsequently increasing the likelihood of errors. It has been reported that potentially harmful ME are three times more common in the paediatric population than in adults (Kaushal *et al.*, 2001). Irrational use of drugs also causes an increase in morbidity and mortality rates, growth impairment due to suboptimal treatment outcomes, poor quality of life, disease spread, prolongation of illness, increased

treatment cost and wastage of limited resources in public and private health sectors. Moreover, irrational drug use may ultimately pose a threat in the emergence of drug resistance (Agabna *et al.*, 2014).

Hence, monitoring of prescriptions and evaluations of drug prescribing patterns can help identify problems associated with irrational drug use and provide feedback to prescribers so as to create awareness and put mechanisms in place to curb the problem.

1.3 Rationale of the study

Promotion of appropriate and safe drug delivery in children is the need of the hour globally. With a rise in health care costs, lack of consistency in treatment therapy and the increase in drug resistance, monitoring and controlling drug use is of upmost prominence. Regular evaluation of prescribing practices is essential to identify the areas requiring improvement and to increase awareness among prescribers of possible errors that may occur in their daily practice (Afify *et al.*, 2015). PPMS provide baseline data regarding prescribing patterns as well as assist in planning prospective studies on drug usage. Moreover, evaluating prescription patterns gives an insight into the nature of health care delivery system, which has a significant impact on clinical and economic outcomes (Horace and Ahmed, 2015). PPMS is of particular importance in paediatric patients as it emphasis on accurate diagnosis and effective treatments by selecting suitable and age appropriate drug regimens, which minimizes the risk of ADRs, ME and prescribing errors (Kagitapu *et al.*, 2016).

Majority of PPMS in South Africa have been conducted mainly on adults, with only a limited number of studies carried out in the paediatric population. From the few available studies, the majority were conducted on inpatients. Studies evaluating prescription patterns in paediatrics, especially those focusing on outpatients is therefore needed. The results from this study on prescription patterns will help identify problems associated with prescribing practices and STGs compliance. This study will help establish a baseline regarding prescribing indicators such as average number of drugs per prescription to evaluate level of polypharmacy, extent of prescribing by generic name, level of antibiotic prescribing and determine the extent of compliance of prescribed treatments with STGs. Based on the findings, recommendations will be provided on the current prescribing practice which can assist in designing educational programs suitable for integration in daily practice to improve rational prescribing and drug use. Key stakeholders will be able to plan targeted and informed interventions to overcome the identified drug use problems. The findings of this study will also help prioritize some disease conditions that might need urgent interventions to improve compliance with STGs.

1.4 Research Questions

This study focused on the following research questions:

The main research question: What is the prescription pattern in the outpatient paediatric department and to what extent is the prescribing pattern in accordance with the paediatric STGs/EML.

The specific research questions:

- For which disease conditions, occurring in the paediatric population are drugs prescribed?
- What drugs are most often prescribed, according to therapeutic classes?
- To what extent are the prescribed drugs appropriate in the paediatrics according to STGs?
- To what extent are drugs prescribed from the EML?
- What is the average number of drugs per prescription for a patient?

1.5 Aims and Objectives of the Study

The aim of the study was to evaluate the prescription patterns in outpatient paediatrics at a public sector tertiary hospital in compliance with STGs/EML.

The specific objectives of the study were:

- To identify the disease conditions that drugs are prescribed in the paediatric population.
- To determine the drugs prescribed most often according to therapeutic classes.
- To establish if the prescribed drugs are appropriate in the paediatric population according to STGs.
- To determine the extent to which drugs are prescribed from the EML.
- To determine the average number of drugs per prescription for a patient.

1.6 Research Methodology

1.6.1 Study Design

This was a retrospective descriptive study, based on analysis of randomly sampled paediatric patient files. The loose criteria model is a method adopted from a report by the Ministry of Health and Social Services of Namibia and Systems for Improved Access to Pharmaceuticals and Services (SIAPS). The loose criteria used in the assessment indicated that "drugs were prescribed as per the guidelines, but with the use of some additional drugs (vitamins and analgesics) or, alternatively, the treatment was not exactly as the STGs dictate, with some variation in dosing and administration" (Akpabio *et al.*, 2014).

1.6.2 Study setting and data source

The study was conducted at a public sector tertiary hospital situated in KwaZulu-Natal, South Africa. Paediatric outpatient files containing prescriptions dated between June 1, 2016 and May 30, 2017 were used to select a study sample. A systematic sampling technique was used to minimize bias in the selection process and to ensure equal representation of samples. All patients aged 12 years and younger, attending the paediatric outpatient department, for whom prescriptions were written were included in the study. Data regarding demographics such as age, gender, weight and diagnosis as well as drug details namely, drug name (generic or brand-name), dose, dosage form, frequency and duration of treatment were captured using MS Excel ®2016.

1.6.2.1 Inclusion criteria

- All outpatient paediatric files dated between June 1, 2016 and May 30, 2017.
- All paediatric patients ages 12 years and younger.
- All patients who attended the paediatric outpatient department, for whom prescriptions were written for were included in the study.

1.6.2.2 Exclusion criteria

- Paediatric patient files of admitted inpatients.
- Pediatric patients older than 12 years of age.
- Patient files with unclear prescriptions (illegible writing).
- Patient files containing no prescriptions were excluded from the study.

1.6.3 Sampling technique and sample size

A systematic sampling technique was used in this study in order to minimize bias in the selection process and to ensure equal representation of samples. Sample size calculation was based on the average number of paediatric patients attending the outpatient department per month (approximately 2,000 patients) yielding an estimated annual number of 24,000 patients. The confidence interval was set at 95% and standard margin of error was 5%, which resulted in a sample size of 379. Patients files which did not meet the inclusion criteria were excluded resulting in a final sample size of 327. The Quasi-random systemic sampling technique was employed whereby, every 73th patient file was selected until the total the sample size was reached.

1.6.4 Data collection

Data collection took place between the period of November 18 - December 28, 2017. A pre-designed MS Excel ®2016 spread sheet was used to capture the relevant extracted data regarding patient demographics such as age, gender, weight and diagnosis as well as drug details containing drug name

(generic or trade name), dose, dosage form, frequency and duration of treatment drug (Appendix 7). Data collection was conducted retrospectively in the medical record office after receiving permission from the hospital administration and the hospital medical records officer in charge.

1.6.5 Data analysis

Data analysis was performed using Statistical Package for Social Sciences® (SPSS®) version 25 and Minitab® version 18. Continuous variables such as patient age and weight were summarised using mean ± standard deviation (SD), whereas medians and interquartile ranges (IQR) were used for highly skewed data and compared using Wilcoxon-Mann-Whitney test as appropriate. Shapiro-Wilk's test for normality was used to determine if the continuous variables were normally distributed. Categorical variables such as gender were summarised using proportions and percentages and compared using Pearson's Chi-square test and Fisher's exact test as appropriate. A multivariate logistic regression test was used to determine the relationship between patient demographic characteristics and the likelihood of treatment compliance with STGs. All levels of significance were kept at 0.05.

1.7 Summary

This chapter provided the background on rational drug use and problems associated with irrational prescribing globally and in South Africa that led to conduct this study. The aim of the study was identified and the objectives of the study were clearly outlined. The chapter described the problem statement, the rationale of the study and the brief methodology used in the study. The next chapter discusses the literature review as related to the study topic.

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CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter provides an overview of various studies conducted on prescription patterns, WHO prescribing indicators, treatment guidelines and essential medicines. The context of this literature review is set by first providing an overview of irrational prescribing followed by discussion on irrational prescribing in paediatrics, the consequences of irrational prescribing, the cost implications of irrational drug use and concludes with approaches to optimizing rational drug use.

2.2 Irrational prescribing

Irrational prescribing is prevalent across nations, hospitals and healthcare setups, which is not only a growing concern in developing countries, but also a global menace (Garg *et al.*, 2014). Generally, irrational prescribing is said to have occurred when drugs are not prescribed according to evidence-based guidelines which ensure the safe, effective and economic usage of drugs (Agabna *et al.*, 2014). According to policy perspective on medicines by WHO (2002), factors that contribute to irrational use of drugs can be classified into three groups, namely:

- Health professional related factors arising from inadequate or lack of continuing education, heavy patient load, lack of drug information, inaccurate diagnosis and lack of compliance with treatment guidelines.
- Health infrastructure related factors caused by poor pharmaceutical supply systems, poor pharmaceutical legislative systems regulating drug registration and usage, scarcity of skilled workforce and shortage of drug.
- Patient related factors influenced by misleading information and beliefs regarding drugs and treatment as well as cultural and religious influences (WHO, 2002a).

2.3 Irrational prescribing in paediatrics

Rational drug use is important for all drug users, but it is of paramount importance for children as they are particularly vulnerable to possible adverse effects of drugs (Yewale and Dharmapalan, 2012). Rational drug use implies that patients receive medication appropriate to their needs in doses that meet their individual requirements, for an adequate period of time and at the lowest cost to them and their community (WHO, 2002a). Unfortunately, irrational drug use is a widespread occurrence in the paediatric population. Although there are no paediatric specific definitions regarding rational drug use to date, Gazarian M. (2009) states the key component to achieve rational therapy in paediatric settings requires the availability of essential drugs with appropriate standards of quality, safety and efficacy alongside with implementing policies which discourage withdrawal of important paediatric drugs from the market unless due to safety or other justifiable reasons. Gazarian further stresses the employment of more systematic prescription monitoring and drug utilization studies are critical in optimizing rational drug use in paediatric population (Gazarian, 2009).

In the past, there have been several tragedies associated with the use of unsafe and unapproved medications in children. The most notable is the grey baby syndrome which caused cardiovascular failure in neonates as a result of potential side effect of chloramphenicol use, and more recently sulfonamide induced kernicterus which caused severe brain damage in newborns suffering from pneumonia or sepsis (Allegaert and Anker, 2014), (WHO, 2007). These events subsequently led to the strengthening and revision of various pharmaceutical legislations. For instance, the implementation of the Modernization Act in 1997, the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003 by the Food and Drug Administration (FDA) (Corny *et al.*, 2015). These complementary federal laws mandate that almost all new drugs and certain approved drugs must be studied in children for approved use of the product and that applications for new drug developments must include adequate paediatric study results (Neville, 2014). Similarly, the European Union passed legislative and regulatory changes that would come into effect in 2007. This aimed to improve the availability of drugs for children, ensure drugs are of high quality, researched and authorised for use in children without subjecting children to unnecessary clinical trials. The United Kingdom and Australia have also published prescribing information for drug use in children (Finney, 2011), (Bracken *et al.*, 2018).

One of the most prevalent practices affecting rational drug use in the paediatric population is off-label prescribing. The term off-label prescribing refers to the use of drugs for indications which are not described or not covered by the product licence (FDA, 2018). According to the European Medicines Agency (EMA), majority of the drugs used to treat children are off-label and not licensed for use (EMA, 2016). A study by Corny et al. (2015) focusing on off-label use among paediatric patients in Europe showed that 18% - 66% of inpatients and 10.5% - 37.5% of outpatients were prescribed off-label drugs (Corny *et al.*, 2015). A study by Santosa L. and Heineck I. (2010) conducted to determine the extent of off-label drug prescribing at a general paediatric inpatient hospital in Brazil reported 38.9% of the prescriptions presented at least one off-label drug (Santos and Heineck, 2012). Another study by Bhadiyadara et al. (2015) conducted in India also reported that 10.1% of the prescriptions assessed contained off-label drugs (Bhadiyadara *et al.*, 2015). Furthermore, a prospective study carried out at a tertiary care hospital in Ethiopia showed 75.8% of the prescriptions were used in an off-label manner (Tefera *et al.*, 2017)

Another widespread practice presenting a particular threat to rational drug therapy in paediatric settings is medication error (ME). The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defines ME as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such errors may be related to professional practice, health care products, procedures or health systems" (NCCMERP, 2018). ME can occur during the process of drug prescribing, transcribing, labelling, packaging, dispensing, preparing or administering, however in the paediatric setting majority of ME are likely to occur during the prescribing and preparing phase (Gokhul, Jeena and Gray, 2016). Most paediatric dosages are adjusted on the basis of the patient's weight and expressed in milligrams of medication per kilogram body weight. However, the weights of paediatric patients can change dramatically over a short period of time especially in small infants, leading to frequent recalculations of doses and potential ME (Chua, Chua and Omar, 2010),

Studies focusing on ME have been conducted since the early 1960s, however a report issued by the U.S. Institute of Medicine in 1999 estimating that as many as 98,000 people die in hospitals each year as a result of ME prompted a push for patient safety and attention on this clinically hazardous problem (Kohn, Corrigan and Donaldson, 1999). A survey conducted in the United Kingdom aiming to identify the incidence of prescribing and administering errors among paediatric patients showed an overall prescribing error rate of 13.2% with incomplete prescriptions and use of abbreviations as the most common error (Ghaleb *et al.*, 2010). A prospective observational study at a tertiary care hospital in South Africa detected prescribing error at 47%, of which incorrect dosing accounted for 34%, followed by medication omission errors at 18.5% (Truter, Schellack and Meyer, 2017). Another study conducted in paediatric patients by Gokhul et al. (2016) at a tertiary hospital in South Africa found among 117 children admitted, 111 were exposed to at least one ME of which 89.2% of the errors occurred during

prescribing with 10.0% having an approximate 10-fold increase or decrease from the appropriate dose (Gokhul, Jeena and Gray, 2016).

2.4 Consequences of irrational prescribing in paediatrics

While drugs save millions of lives globally each year, their irrational and indiscriminate use can pose an increasing threat. When drugs are used inappropriately, the risks of harmful effects such ADRs and drug resistance is increased significantly (Ofori-Asenso and Agyeman, 2016). A study conducted in the United States at a paediatric hospital found that multi-drug resistant infections increased from 0.2% in 2007 to 1.5% in 2015. This increase adversely imposes pressure on the choice of appropriate first-line antibiotics (Meropol, Haupt and Debanne, 2017). Another study by Horace and Ahmed (2015) focusing on polypharmacy in paediatric patients also revealed that the rates of acute and chronic diseases in the paediatric population have been steadily increasing and medications used to treat these conditions have also shown a proportional increase (Horace and Ahmed, 2015). Indiscriminate prescribing can also expose patients to develop drug dependence and exert a psychological effect on patients who may conclude that there is "a pill for every ill", causing an excessive cycle of drug dependant therapy (Ofori-Asenso and Agyeman, 2016). Furthermore, irrational drug use increases morbidity and mortality rates, exacerbation or prolongation of disease, growth impairment due to suboptimal treatment outcomes, patient distress and harm, in addition to unnecessary wastage of resources and exhaustion of limited health budgets (Agabna *et al.*, 2014), (Ranganathan and Gazarian, 2015).

Children are subjected to many of the same disease conditions that adults suffer from and are often treated with off-label or unlicensed drugs. The consequences of this common practice can place children at a greater risk regarding exposure to potential ADRs (Neville, 2014). The WHO defines ADRs as any noxious, unintended and undesired effect of a drug that occurs at normally used doses for prophylaxis, treatment or diagnosis of a disease, or for the modification of physiological function (WHO, 2002b). A study reported by Napoleone E. (2010) shows ADRs in the United States were the cause of 244, 000 outpatient visits in paediatrics under 15 years of age. The study also indicated that half of the registered ADRs occurred in children younger than 4 years of age, and the potential risk of developing ADRs among children under 5 years of age was 4 times higher than children who attend schools (Napoleone, 2010). Surveillance studies reporting ADRs in paediatric patients using national pharmacovigilance databases conducted in Denmark and Spain reported ADRs categorised as "severe" in 42% and 37% of the study patients respectively (Aagaard *et al.*, 2010), (Aldea *et al.*, 2012). A recent study conducted in 2018 by Makiwane et al. carried out at a tertiary hospital in South Africa reported the rate of paediatric hospital admissions due to ADRs was 31%. The study further indicated that 11.5% of the ADRs were categorised as "severe" (Makiwane *et al.*, 2018).

2.5 Cost implications of irrational medicine use

Irrational drug use is a major problem facing many health care settings throughout the world, particularly in developing countries where the proportion of national health budgets spent on drugs ranges between 30 - 40% (Tamuno and Fadare, 2012). According to the medicine use report from the Institute for Human Data Science, the global drug spending in 2018 was 1.2 trillion U.S. dollars (USD) and is expected to reach 1.5 trillion USD by 2023 (Institute for Human Data Science, 2019). A study by the Institute for Healthcare Informatics reported that a total global expenditure of 269 billion USD was spent on cases related to non-adherent drug use, while 54 billion USD and 42 billion USD was spent on antibiotic misuse and medication error respectively. The study further indicated that worldwide up to 500 billion USD is spent annually on avoidable irrational use of drug (Intercontinental Marketing Services (IMS), 2012). This situation sharply contrasts the core principals of rational drug use which dictates drugs to be cost effective and safe (WHO, 2011).

2.6 Approaches to optimize rational drug use

2.6.1 Clinical guidelines and STGs/EML

It is vital to know the extent of irrational drug use and the associated elements in order to develop effective strategies and interventions to promote rational use. In South Africa, the provision of pharmaceutical services is guided by the National Drug Policy (NDP), which was adopted in 1996 in order to ensure rational, efficient and cost-effective supply and use of drugs (DOH, 1996). Clinical guidelines (STGs and EML) consist of systematically developed statements designed to assist and guide prescribers in making appropriate decisions regarding diagnosis, management and treatment for specific clinical circumstances. Evidence-based clinical guidelines are crucial to promote the delivery of high quality health care and the appropriate utilization of drugs. They provide a benchmark of acceptable diagnosis and treatment recommendations against which comparison of actual treatments are made (SIAPS, 2015).

Interestingly, guidelines have been in use for as long as the art of healing has existed. Traditional healers compiled their list of cures and developed standard set of treatments which they passed from generation to generation. In modern medicine, these guidelines are referred to as STGs, standard treatment schedules, standard treatment protocols and therapeutic guidelines (Hassan *et al.*, 2017). STGs are systematically developed statements comprising a list of preferred pharmaceutical and non-pharmaceutical treatments for common health problems designed to assist prescribers in making appropriate decisions for specific clinical circumstances (Management Sciences for Health, 2012). The implementation of STGs in all health care systems is of upmost importance in order to harmonize the numerous treatments that are available (Gopalakrishnan, Udayshankar and Rama, 2014).

STGs improve the overall rational use of drugs as they provide standardized guidance to prescribers, listing the most appropriate treatments based on expert consensus on most effective and economical treatments available (Alamgir and Ahmed, 2015). STGs are considered as one of the most effective tools in the promotion of evidence-based drug therapy as it aids in regulating the tension between healthcare cost and quality. STGs can be employed in a wide range of settings to promote effective and efficient healthcare such as guiding the introduction of new procedures or services, promoting effective health care extending from primary up to tertiary care facilities and encouraging the adoption of cost-effective interventions (Mazrou, 2013).The South African paediatric STGs/EML was initially introduced in 1998 and has currently been updated to its fourth edition and is being used in all nine provinces where it caters for the common disease conditions (DOH, 2017).

2.6.2 Essential Medicines

Essential medicines are those that satisfy the priority health needs of a population, selected with due regard to disease prevalence and public health relevance, evidence of clinical efficacy and safety of the product. Essential medicines should be available at all times according to the setting of functioning health systems in sufficient amounts, in proper dosage forms, with assured quality and at a price patients and the community can afford (WHO, 2011) . The initial list of essential medicines proposed by the WHO in 1977 aimed to assist countries in selecting and procuring priority medicines, assuring good quality and reasonable cost. The original list included 186 essential medicines with the concept of being flexible and adoptable with varying situations, under the notion which drugs were regarded as essential remained a national responsibility. Since then, the WHO has been updating the list every two years, with the latest revision published in 2017 containing around 457 essential medicines (WHO, 2017)

However, it was not until 2006 the WHO began to lay foundations for improving access to essential medicine addressing the needs of paediatric patients. It was evident that enhancing the safety and efficacy of child medicine was crucial in improving paediatric health care and reducing mortality (American Acadamy of Pediatrics, 2011). With approximately 80% of the marketed drugs in the world not approved by the FDA for paediatric use, the goal was to prioritize available drugs from the current EML (Finney, 2011). As a result, in 2007 the “better medicine for children” act was adopted and the first paediatric EML was issued. Since then the paediatric EML has been revised three times and the current fourth edition is currently in effect (Turner *et al.*, 2014).

The government of South Africa clearly outlines its commitment to ensure that the paediatric population receives access of care to the highest quality as indicated in the health objectives of the NDP. In South Africa, the criteria for the selection of essential drugs for primary health care is based on the WHO guidelines for EML which includes the following points: availability of sufficiently proven scientific data regarding effectiveness of the drug, any drug included in the EML should have a substantial safety risk/benefit ratio and combination products will be included as an exception where patient compliance becomes an important factor (DOH, 2017).

2.6.3 Prescription Pattern Monitoring Studies (PPMS)

Drug therapy is considered to be a major component of paediatric health care setting. Paediatric patients require more attention while prescribing in order to avoid drug resistance, ADRs as well as drug-drug reactions. An effective step should be taken for rational use, based on an accurate diagnosis and optimum course of therapy regimen especially in the paediatric population. PPMS promote drug utilization by focusing on drug prescribing, dispensing and administration. PPMS encourage the appropriate use, reduction and abuse of monitored drugs (Rajappa and Shaji, 2015). PPMS also provide guidance and support to prescribers, dispensers and the general public as a whole on rational use of drugs, facilitate collaborations and improve working relationship with other key stakeholders and organizations to achieve appropriate utilization of drugs (Kandula et al., 2017). Prescription patterns explain the extent and profile of drug use, trends, quality of drugs, and compliance with regional, state or national treatment guidelines, usage of drugs from EML and use of generic drugs. Some of the core objectives of PPMS include: promoting optimal treatment therapy, ensuring pharmaceutical therapy meets the requirements of the current standards of care, identifying specific problems related with drug use that require further assessment and controlling the pharmaceutical cost (Jain *et al.*, 2015).

With a rise in health care costs globally, lack of consistency in treatment therapy and the increase in drug resistance, monitoring and controlling drug use is of upmost concern. Regular evaluation of prescribing practices is essential to identify the areas requiring improvement and to increase awareness among prescribers of possible errors that may occur in their daily practice. PPMS provide baseline data regarding prescribing patterns as well as assist in planning longitudinal prospective studies on drug usage. Moreover, evaluating prescription patterns gives an insight into the nature of the health care delivery system, which has an impact on the clinical and economic outcomes (Al Balushi *et al.*, 2013).

2.6.4 WHO indicators used to measure prescribing patterns

Drug use in health facilities can be assessed through objectively measuring the extent of usage by means of core prescribing indicators. The drug use indicators were developed by the WHO in conjunction with the International Network for the Rational Use of Drugs (INRUD) to assist in investigating drug use in health care facilities. These indicators serve as tools for assessing key aspects of pharmaceuticals used in healthcare facilities (WHO, 1993). The five prescribing indicators include: average number of drugs per encounter, percentage of drugs prescribed by generic name, percentage of encounters with an antibiotic prescribed, percentage of encounters with an injection prescribed and percentage of drugs prescribed from formulary list. These indicators measure the performance of prescribers in key areas concerning rational drug use based on clinical encounters at healthcare facilities of different disease conditions (WHO, 1993).

2.6.4.1 Average number of drugs per encounter

This indicator is used to assess the degree of polypharmacy. The WHO standard value for this indicator is 1.6 - 1.8 (Isah *et al.*, 2008). Studies done in many countries across the world have reported varying results on the average number of drugs prescribed per encounter. Low values of average drugs per encounter were reported in studies conducted in Ethiopia (1.33) and Italy (1.40), while acceptable value of 1.90 was documented in India. Studies conducted in Tanzania (2.80), Saudi Arabia (3.0), Sierra Leone (3.77), Brazil (5.40) and Spain (7.40) reported a higher average value compared to the standard value recommended by WHO. Table 1 presents summarised studies from countries that reported on average number of drugs prescribed per encounter in paediatric patients. The average number of drugs largely depend on disease patterns, policies and treatment guidelines and therefore may vary from country to country and over time (Mahmoud, Kheder and Ali, 2014). Factors contributing to higher number of drug prescribing may include the unavailability of clinical treatment guidelines, lack of prescribers familiarity with treatment guidelines as well as the lack of recurrent medical training and education of the prescribers (Alili-Idrizi, Dauti and Malaj, 2015).

Table 1. Summary of studies that reported on average number of drugs per encounter in paediatric patients.

Country of study	Total number of drugs prescribed	Average number of drugs per encounter	References
Ethiopia	510	1.33	(Teni *et al.*, 2014),
	1,117	4.50	(Agalu and Mekonnen, 2012)
Italy	8,805	1.40	(Cazzato *et al.*, 2001)
India	759	1.90	(Sharma and Oommen, 2015),
	1,285	2.29	(Jose and Devassykutty, 2016),
	1627	3.74	(Thomas *et al.*, 2014)
Gambia	5,277	2.20	(Risk *et al.*, 2013a)
Oman	-	2.30	(Al Balushi *et al.*, 2013)
Guyana	-	2.50	(Sharma *et al.*, 2016)
Bahrain	5,745	2.52	(Khaja *et al.*, 2007)
United Arab Emirates	1,336	2.60	(Sharif *et al.*, 2015)
Nigeria	526	2.60	(Fadare *et al.*, 2015)
	1,115	3.80	(Nduka *et al.*, 2017)
Sudan	20,482	2.77	(Mahmoud, Kheder and Ali, 2014)
Tanzania	1,574	2.80	(Mambile *et al.*, 2016)
Saudi Arabia	-	3.0	(Gupta *et al.*, 2013)
Sierra Leone	-	3.77	(Cole, James and Kargbo, 2015)
Brazil	2,026	5.40	(Santos and Heineck, 2012)
Spain	601	7.40	(Blanco-Reina *et al.*, 2016)

2.6.4.2 Percentage of drugs prescribed by generic name

This indicator assesses the tendency of prescribers to prescribe using generic drugs (international non-proprietary names) as opposed to brand drugs (proprietary names). The WHO standard value for this indicator is 100% (Isah *et al.*, 2008). Varying percentages ranging from 3.27 to 98.40% were reported from studies done in different countries across the world (Table 2). The percentage of drugs prescribed using generic names was very low in studies conducted in Italy (3.27%), Nigeria (7.30%) and Pakistan (10.0%). However, high percentages were documented in studies carried out in Sierra Leone (71.0%), Gambia (74.8%0) and India (98.40%). Generic prescribing promotes rational drug use as it ensures use of common terminologies between prescribers and dispensers in a health care facilities, thereby reducing dispensing errors (Akpabio *et al.*, 2014). Possible reasons contributing to low generic prescribing could be prescriber's doubt regarding the efficacy and bioavailability of generic formulations, poor knowledge of drug formularies as well as unawareness of price variations between generic and branded drugs (Mulwa *et al.*, 2015).

Table 2. Summary of studies that reported on percentage of drugs prescribed by generic names in paediatric patients.

Country of study	Percentage of drugs prescribed by generic name	References
Italy	3.27	(Cazzato *et al.*, 2001)
Nigeria	7.30	(Oshikoya, Chukwura and Ojo, 2006)
	62.30	(Nduka *et al.*, 2017)
	68.90	(Fadare *et al.*, 2015)
India	7.80	(Naveen, Ramesh and Teki, 2018)
	19.60	(Thiruthopu *et al.*, 2014)
	20.0	(Kumar, Ram and Ramasamy, 2013)
	60.20	(Sharma and Oommen, 2015)
	98.40	(Jose and Devassykutty, 2016)
Pakistan	10.0	(Nesar *et al.*, 2018)
Guyana	30.0	(Sharma *et al.*, 2016)
United States	40.60	(Chen and Wu, 2008)
Yemen	41.0	(Alshakka *et al.*, 2016)
Oman	45.10	(Al Balushi *et al.*, 2013)
Bangladesh	49.0	(Alamgir and Ahmed, 2015)
Sierra Leone	71.0	(Cole, James and Kargbo, 2015)
Gambia	74.80	(Risk *et al.*, 2013b)
Ethiopia	82.0	(Agalu and Mekonnen, 2012)
	83.19	(Somasundaram *et al.*, 2015)
	97.5	(Feleke, Yenet and Lenjisa, 2013)
Tanzania	85.80	(Mambile *et al.*, 2016)
United Arab Emirates	100.0	(Sharif *et al.*, 2015)

2.6.4.3 Percentage of encounters with an antibiotic prescribed

This indicator is used to assess the overall use of antibiotics. According to the WHO, 15 – 25 % of prescriptions with antibiotics is expected in most developing countries where infectious diseases are more prevalent (WHO, 2011). Percentages above this standard value indicate over prescription of antibiotics. Most prescription surveys conducted in different countries reported over use of antibiotics. Among the 22 studies reviewed in this study, Mozambique (97.60%) had the highest percentage of antibiotic prescribing followed by Germany (90.70%), Ethiopia (86.40%) and Yemen (84.20%) as shown in Table 3. Possible factors that could contribute to high antibiotic prescribing in children include: demand or expectations from parents to use antibiotics, diagnostic uncertainty as most patients with viral and bacterial infections often present similar symptoms and workload as physicians can be pressured while formulating treatment plans (Alili-Idrizi, Dauti and Malaj, 2015).

Table 3. Summary of studies that reported on percentage of encounter with an antibiotic in paediatric patients.

Country of study	Percentage of encounter with an antibiotic prescribed	References
Australia	10.10	(Yan *et al.*, 2019)
Brazil	13.52	(Santos and Heineck, 2012)
Spain	16.50	(Santander *et al.*, 2018)
	80.0	(Blanco-Reina *et al.*, 2016)
India	25.70	(Sharma and Oommen, 2015)
	33.0	(Sireesha *et al.*, 2016)
	38.70	(Kagitapu *et al.*, 2016),
	41.0	(Dutta, Bhattacharjee and Devi, 2017),
	50.56	(Pradeepkumar *et al.*, 2017),
	73.18	(Jose and Devassykutty, 2016)
Latvia	26.0 – 38.0	(Sviestina and Mozgis, 2018)
United States	28.0	(Gerber *et al.*, 2015)
Nigeria	41.40	(Oshikoya, Chukwura and Ojo, 2006),
	71.10	(Fadare *et al.*, 2015)
Ethiopia	44.90	(Agalu and Mekonnen, 2012)
	86.40	(Kebede *et al.*, 2017)
Denmark	46.0	(Kinlaw *et al.*, 2017)
Gambia	54.10	(Chaw *et al.*, 2018)
China	67.76	(Zhang *et al.*, 2018)
Yemen	84.20	(Alshakka *et al.*, 2016)
Germany	90.70	(Neubert *et al.*, 2010)
Mozambique	97.60	(Monteiro *et al.*, 2017)

2.6.5 Institutional Guidelines- National Drug Policy

National Drug Policy (NDP) is a written document specifying medium to long term goals set by the government for the pharmaceutical sector highlighting their comparative importance and main strategies for attaining them. It provides a framework for coordinating activities in the public and private pharmaceutical sectors. The South African NDP was introduced in 1996 in response to the lack of equity in access to essential drugs, rising drug prices, increase in irrational drug use and evidence of cost-ineffective procurements. The NDP is intended to be incorporated into the national health system in order to ensure the goals and objectives are addressed in broad health plans and to help allocate resources efficiently. Some of the key goals of the NDP currently in effect include: ensuring the availability and accessibility of essential drugs to all citizens, ensuring the safety, efficacy and quality of drugs and promoting the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training and education (DOH, 1996).

2.6.6 Pharmaceutical and Therapeutics Committees

The establishment of pharmaceutical and therapeutics committees (PTCs) has been advocated by the WHO as one of the vital interventions to promote rational drug use. PTCs are committees designated to ensure the safe and effective use of drugs in health facilities. Their role is to optimize rational drug use by monitoring and evaluating the clinical use of pharmaceuticals, developing policies for managing drug use and administering the formulary system (DOH, 2015). In the South African context, PTCs have crucial roles in actively promoting paediatric drug use by assisting in the development of treatment guidelines, conducting regular assessments such as review of ADRs and prescribing errors, investigating the problems reported and addressing the identified problems (Management Sciences for Health, 2012). A recent study conducted by Matlala et al. (2017) at a public hospitals in the Gauteng province, identified PTCs as pivotal models to promote rational drug use in health facilities to ensure rational, efficient and cost-effective drug use (Matlala *et al.*, 2017).

2.7 Summary

This chapter provided a literature review of studies conducted globally, keeping in view the objectives of the study. It provided an overview of irrational drug use in paediatrics, the consequences of irrational prescribing and approaches to optimizing rational drug use. It further included a summary of different studies on prescribing indicators namely, average number of drugs per encounter, average number of generic prescribing and average number of antibiotic prescribing. The following chapter includes the results and discussion of the study presented in manuscript format, submitted to the International Journal of Pediatric and Adolescent Medicine.

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CHAPTER 3
FIRST MANUSCRIPT SUBMITTED FOR PUBLICATION

3.1 Introduction

This chapter describes the general findings and discussion of the results of the study and is represented in the form of a manuscript titled "Prescribing Patterns in an Outpatient Paediatrics Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa". This manuscript has been submitted to the *"International Journal of Pediatrics and Adolescent Medicine"* for publication.

3.2 Manuscript one

Prescribing Patterns in Paediatrics Outpatient Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa.

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Declaration of interest

The authors declare that they have no conflicts of interest.

"Prescribing Patterns in Paediatrics Outpatient Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa"

ABSTRACT

Background:

Prescription pattern monitoring studies are tools for assessing the prescribing and dispensing of drugs. They help in explaining the extent, trend and compliance of drug prescribing and play a vital role in promoting rational drug use. There is limited information on drug prescribing in the paediatric population in South Africa. The aim of this study was to evaluate the drug prescribing patterns in paediatric outpatients department at a tertiary care hospital in Kwa-Zulu Natal, South Africa.

Methods:

A descriptive, retrospective study was conducted at the paediatric outpatient department of a tertiary care hospital from November 18 - December 28, 2017. Paediatric outpatient files containing prescriptions dated between June 1, 2016 and May 30, 2017 were used. Patient demographics, diagnosis, and drugs prescribed were extracted from the patient files and captured using Microsoft Excel® 2016. Data was analyzed using Statistical Package for Social Sciences® (SPSS®) version 25 and Minitab® version 18 statistical software.

Results:

A total of 327 patient files comprised of 193 (59.02%) male and 134 (40.98%) female patients were assessed. Majority of the patients were infants 121 (37%) within the age group of 1 month - 1 year. The average age of patients was 3.06 ± 3.21 years, interquartile range 4.33 years. Overall, 845 drugs were prescribed of which 354 (41.89%) were generic. The most frequently prescribed drug groups were antibiotics 155 (18.34%), emollients 118 (13.96%) and analgesics 117 (13.85%). Paracetamol 110 (18.61%) and aqueous cream 63 (10.66%) were amongst the most commonly prescribed drugs items. The percentage of encounters with antibiotics was 35.47% and average number of drugs per prescription was 2.58. The most encountered disease conditions were eczema, acute gastroenteritis, and scabies with frequencies of 41 (30.60%), 17 (12.69%) and 15 (11.19%) respectively.

Conclusion:

There was a high level of antibiotic prescribing pattern among the paediatric outpatients, and penicillin was the most often prescribed. The average number of drugs per prescription identified in this study was higher than that recommended by World Health Organization. The need for training of prescribers and healthcare professionals is of utmost importance in order to promote appropriate use of drugs and overall patient safety.

Key words: Paediatric, prescription patterns, drugs, disease conditions, comorbidities.

List of abbreviations

ADRs- Adverse Drug Reactions; CTM®- Chlortrimeton; EML- Essential Medicine List; GASI- Gastric Acid Secretion Inhibitor; IQR- Interquartile Range; NSAIDs- Nonsteroidal anti-inflammatory drugs; PPMS- Prescription Pattern Monitoring Studies; SD- Standard deviation; STGs- Standard Treatment Guidelines; WHO- World Health Organization.

BACKGROUND

Evaluation of drug prescription patterns is an important aspect of patient care, which also serves as a measure of the quality of health care provided [1]. Prescribing is a complex task which requires diagnostic skills, knowledge of drugs, understanding of clinical pharmacology and communication skills and needs constant monitoring in order to achieve rational drug use [2]. Prescription pattern monitoring studies (PPMS) are tools used in the evaluation of prescribing, dispensing, and distribution of drugs [3]. The focus of PPMS is to describe the profile and quality of drug use, extent of compliance with national guidelines such as standard treatment guidelines (STGs) and essential medicine list (EML) [3]. Despite drugs being highly prescribed for health management in paediatric patients, there is a limited availability of licensed drugs particularly in the appropriate dosage forms [4]. Moreover, drug use in paediatrics is not extensively researched, particularly due to ethical issues surrounding this population [5].

Globally, about 1.9 billion of the world population is under 15 years of age, of which 41% live in Africa [6]. South Africa is a developing country with a projected population of 56.50 million people in 2017, where children under 15 years of age account for 29.60% of the total population [7]. Children in this age range are especially vulnerable to harmful effects of drugs due to their under developed immunological, renal and hepatic systems, which creates pharmacokinetic and pharmacodynamic differences when compared to adults [8][9]. Paediatric patients require specific attention when prescribing medications in order to avoid adverse drug reactions (ADRs), medication errors (ME), drug - drug interactions and drug resistance [10][11].

To the best of our knowledge, majority of PPMS in South Africa have been conducted mainly in adults, and a few in the paediatric population, focusing primarily on inpatients. It has been reported that unlicensed drug prescriptions are used in paediatric treatments. For instance, the proportions of unlicensed drug prescriptions could be as high as 17% in outpatient care [12]. Paediatric outpatients, when compared to paediatric inpatients, usually fail to comply with drug regimen due to less monitoring

of dosing schedules by healthcare personnel [13]. It is known that safe and effective drug therapy is possible only when patients are well informed about the medication and their use [14].

Studies evaluating prescription patterns in children, especially those focusing on outpatients is therefore needed to identify the problems related to drug therapy and irrational drug use. This study focused on evaluating the drug prescribing patterns in paediatric outpatients at a public sector tertiary hospital located in KwaZulu-Natal, South Africa.

METHODS

Study design

This was a retrospective descriptive study, based on analysis of randomly sampled paediatric patient files, conducted in the paediatric outpatient department. This study evaluated the prescription patterns of drugs and assessed the disease conditions. This study was carried out at a tertiary care hospital in KwaZulu-Natal, South Africa.

Data source and study population

Paediatric outpatient files containing prescriptions dated between June 1, 2016 and May 30, 2017 were assessed. A systematic random sampling technique was used to minimize bias in the selection process and to ensure equal representation of samples. The Quasi random sampling technique was employed whereby every 73th patient file was selected until the total the sample size was reached. The files at the outpatient department of all patients aged 12 years and younger, and for whom prescriptions were written for were included in the study. Demographic data including age, gender, weight and diagnoses, as well as drug details such as, drug name (generic or trade name), dose, dosage form, frequency and duration of treatment were captured using MS Excel® 2016.

Statistical analysis

The data were analysed using Statistical Package for Social Sciences® (SPSS®) version 25 and Minitab 18® Statistical Software. Continuous variables such as patient age and weight were summarised using mean ± standard deviation (SD), whereas medians and interquartile ranges (IQR) were used for highly skewed data and compared using Chi-square test. Shapiro-Wilk's test for normality was used to determine whether continuous variables were normally distributed. Categorical variables such as gender were summarised using proportions and percentages and compared using Pearson's Chi-square test and Fisher's exact test as appropriate. From the total number of drugs in this study, drugs with a prescribing frequency of 10 and above were selected for associations between commonly prescribed drugs and age groups. A Pareto test was used to identify drugs that contributed to 80 percent of the most commonly prescribed drugs. A Pareto chart provides an illustration of the Pareto principle, which asserts that 80%

of the observed outcome is produced by 20% of the input variables [15]. Pearson's correlation (r) was used to determine a potential correlation between patient's age and the number of comorbidities and the prescribed drugs.

RESULTS

Demographic characteristics of patients

A total of 327 patient files were evaluated, of which 193 (59.02%) were for male patients and 134 (40.98%) female patients. The average age of patients was 3.06 ± 3.21 years, median of 1.66, and IQR of 4.33 years. Majority of the patients 121/327 (37%) were infants within the age group of 1 month - 1 year, and more than half being male, followed by patients aged 1 to 5 years 119/327 (36.39%). The least number of patient files 17/327 (5.20%) were for neonates up to 1 month. Age was found to be non-normally distributed using the Shapiro-Wilk test of normality (p value < 0.05). The weight of the patients ranged between 2.74 kg to 71.5 kg with an average weight of 14.31 kg ± 9.09 kg (Table 1).

Table 1 Patient characteristics and categories of prescribed drugs.

Independent Variables		**Frequency**	**Percent**
Gender	Male	193	59.02
	Female	134	40.98
	Total	**327**	**100**
Age groups	Neonates (< 1 month)	17	5.20
	Infants (1 month – 1 year)	121	37.00
	Children (> 1 – 5 years)	119	36.39
	School age (> 5 – 12 years)	70	21.41
	Total	**327**	**100**
Weight (Kg)	≤ 10	92	28.13
	11 – 20	100	30.58
	21 – 30	31	9.48
	≥ 31	17	5.20
	No data	87	26.61
	Total	**327**	**100**
Drug groups	Analgesic	117	13.85
	Anesthetic	2	0.24
	Anthelmintic	4	0.47
	Antianaemic	22	2.60
	Antibiotic	155	18.34
	Antiepileptic	8	0.95
	Antifungal	16	1.89
	Antiglaucoma	4	0.47
	Antihistamine	97	11.48
	Antihypertensive	1	0.12
	Antimycobacterials	7	0.71
	Antimyotic	19	2.25
	Antiprotozoal	1	0.12
	Antipruitic	4	0.47
	Antipsoriatic	14	1.66
	Antiretroviral	4	0.47
	Bronchodilator	17	2.01
	Corticosteroid	98	11.60
	Decongestant	34	4.02
	Diuretic	3	0.36
	Emollient	118	13.96
	GASI (Gastric Acid Secretion Inhibitor)	3	0.36
	Laxative	7	0.95
	Scabicide	17	2.01
	Sodium Supplement	25	2.96
	Topical Antiviral	1	0.12
	Viral Vaccine	2	0.24
	Vitamins	28	3.31
	Zinc Supplements	17	2.01
	Total	**845**	**100**

Prescribing patterns

The total number of drugs prescribed was 845, of which 354 (41.89%) were generic drugs prescribed from the EML and 491 (58.11%) non-generic drugs prescribed under trade names which were not listed in the EML. The drug groups most commonly prescribed were antibiotics 155/845 (18.34%) followed by emollients 118/845 (13.96%), analgesics 117/845 (13.85%) and corticosteroids 98/845 (11.60%). Of the 155 antibiotic drugs, 55/155 (35.48%) were penicillins, 40/155 (25.81%) penicillins combined with beta-lactamase inhibitors, 39/155 (25.16%) cephalosporins and 6/155 (3.87%) aminoglycosides. The percentage of encounters with antibiotics was found to be 35.47%.

In order to determine for a possible association between patient age and drug items prescribed, we selected the most common drugs items that had a prescribing frequency of 10 and above which resulted in 22 drug items as presented in Table 2.

Table 2 Common drug items with prescribing frequency of 10 and above (n=591).

No.	Drug items	Frequency	Percentage
1	Paracetamol	110	18.61
2	Aqueous cream	63	10.66
3	Amoxicillin)	51	8.63
4	Chlorpheniramine maleate)	45	7.61
5	Amoxicillin + Clavulanic acid)	40	6.77
6	Chlorpheniramine maleate)	33	5.58
7	Cefadroxil)	27	4.57
8	Emollient cream	26	4.40
9	1% Hydrocortisone cream	23	3.89
10	Sorol Citrate)	21	3.55
11	Fluconazole	19	3.21
12	Saline nose drop	17	2.88
13	Emulsifying ointment	15	2.54
14	0.03% Betamethasone cream	14	2.37
15	Procutan cream	14	2.37
16	5% Sulphur ointment	11	1.86
17	Normal saline nose drop	11	1.86
18	Zinc	11	1.86
19	Cephalexin	10	1.69
20	Cetirizine	10	1.69
21	Folic acid	10	1.69
22	Prednisone	10	1.69
	Total	**591**	**100**

A Pareto test was used to identify drugs contributing to 80 percent from the 22 commonly prescribed drug items, resulting in 12 drug items. Paracetamol 110/591 (18.61%) was the most frequently prescribed drug item, followed by aqueous cream 63/591 (10.66%), Amoxicillin 51/591 (8.63%), Chlorpheniramine maleate 45/591 (7.61%) and Amoxicillin + Clavulanic acid 40/591 (6.77%) as shown in Figure 1.

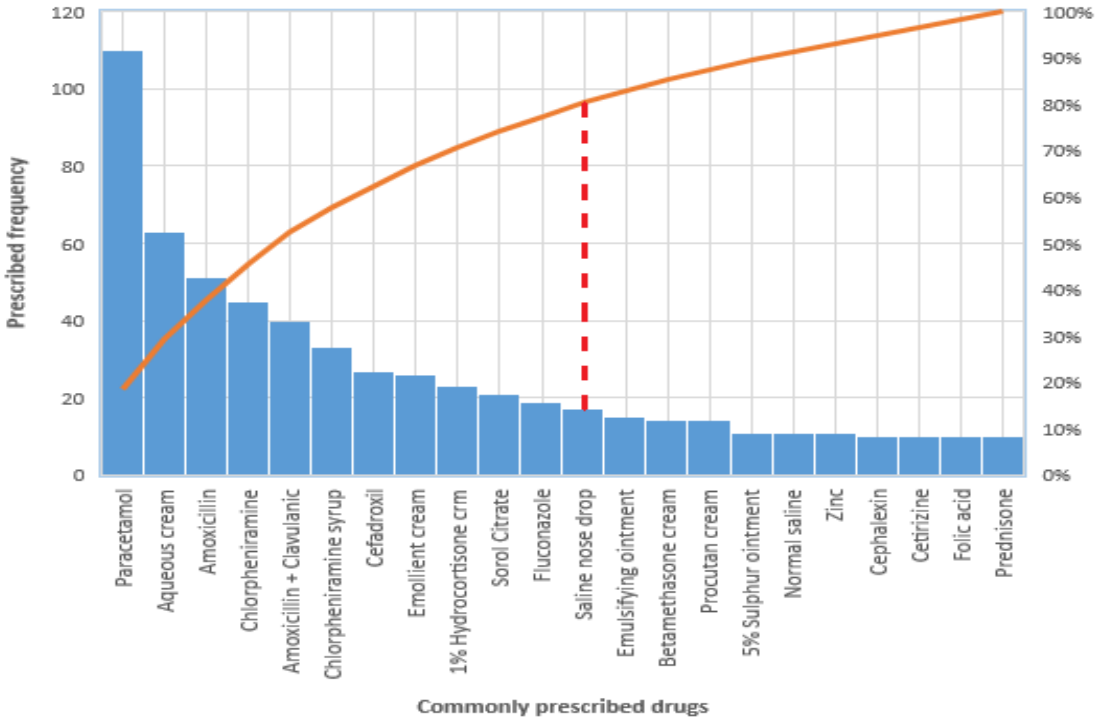

Figure 1 Pareto plot showing the selection of 12 commonly prescribed drug items.

In order to determine for a possible association between patient age and drug items prescribed, a Chi-square test was used which revealed only Paracetamol showed statistically significant association with age (p value = 0.17). No statistically significant association was noted between gender and the commonly prescribed drug items (p value = 0.83).

In this study, the average number of drugs per prescription was 2.58, and the maximum number of drugs found in a single prescription was 9 (Table 3). In terms of routes of administration, oral drugs contributed the highest proportion of the drugs prescribed 532/845 (62.96%), followed by topical preparations 296/845 (35.03%). Rectal and parenteral preparations, each constituting less than 1%, were the least prescribed routes of administration.

Table 3 Distribution of prescriptions with different number of drugs.

Number of drugs per prescription	Number of prescriptions	Percentage
1	78	23.85
2	107	32.72
3	70	21.41
4	41	12.54
5	19	5.81
6	5	1.53
7	6	1.83
9	1	0.31
Total	**327**	**100**
Range	**1 – 9**	
Average number of drugs	**2.58**	

Commonly diagnosed diseases

Among the 327 prescriptions reviewed, a total of 419 disease conditions were identified. Of the 419 disease conditions, the most commonly diagnosed conditions were selected, which resulted in a total of 134 diseases conditions for further analysis.

Eczema 41/134 (30.60%) was the most frequently encountered disease condition, followed by acute gastroenteritis 17/134 (12.69%), scabies 15/134 (11.19%) and tinea capitis 13/134 (9.70%). Nasal congestion and seizure, both with frequency of 7/134 (5.22%) were the least common conditions. Majority of the patients 100/134 (74.63%) did not have comorbidities, while 34/134 (25.37%) had co-occurring conditions ranging from 2 to 4 diseases. Male patients 19/34 (55.88%) showed slightly higher frequency of comorbidities in comparison to female patients 15/34 (44.12%). Table 4 depicts the extent of comorbidities in the commonly diagnosed disease conditions among male and female patients.

Table 4 Comorbidities in the commonly diagnosed disease conditions among male and female patients

Disease conditions	Disease conditions with no comorbidities		Disease conditions with comorbidities		Gender			
	Frequency	Patient Mean age, (± SD)	Frequency	Patient Mean age, (± SD)	Male		Female	
					Disease conditions with no comorbidities	Disease conditions with comorbidities	Disease conditions with no comorbidities	Disease conditions with comorbidities
Eczema	36	2.54, (2.87)	5	4.50. (2.12)	23	3	13	2
Acute gastroenteritis	12	1.50, (1.73)	5	3.52, (2.62)	9	4	3	1
Scabies	14	3.00, (1.44)	1	2, (-)	11	-	3	1
Tinea capitis	10	4.10, (2.14)	3	4.86, (2.04)	5	1	5	2
Tonsillitis	8	8.19, (10.54)	4	5.75, (2.99)	2	3	6	1
Bronchitis	6	0.69, (0.40)	6	0.60, (0.29)	4	3	2	3
Impetigo	5	2, (-)	5	1.50, (0.71)	-	2	5	3
Seizures	4	2.49, (2.24)	3	3.33, (2.31)	2	3	2	-
Nasal congestion	5	1.00, (0.37)	2	3.5, (2.12)	4	-	1	2

In order to determine a possible correlation between patient age, number of comorbidities and drugs prescribed, a Pearson's correlation test (r) was used which revealed a negative correlation between patient age and number of comorbidities (r = -0.24, n = 14, p = 0.388). A negative correlation was also observed between patient age and number of drugs prescribed (r = -0.38, n = 14, p = 0.536). However, there was a strong positive correlation between number of comorbidities and the number of drugs (r = 0.79, n= 14, p= 0.001). Figure 2 demonstrates the correlation between number of drugs prescribed and comorbidities diagnosed in relation to patient age.

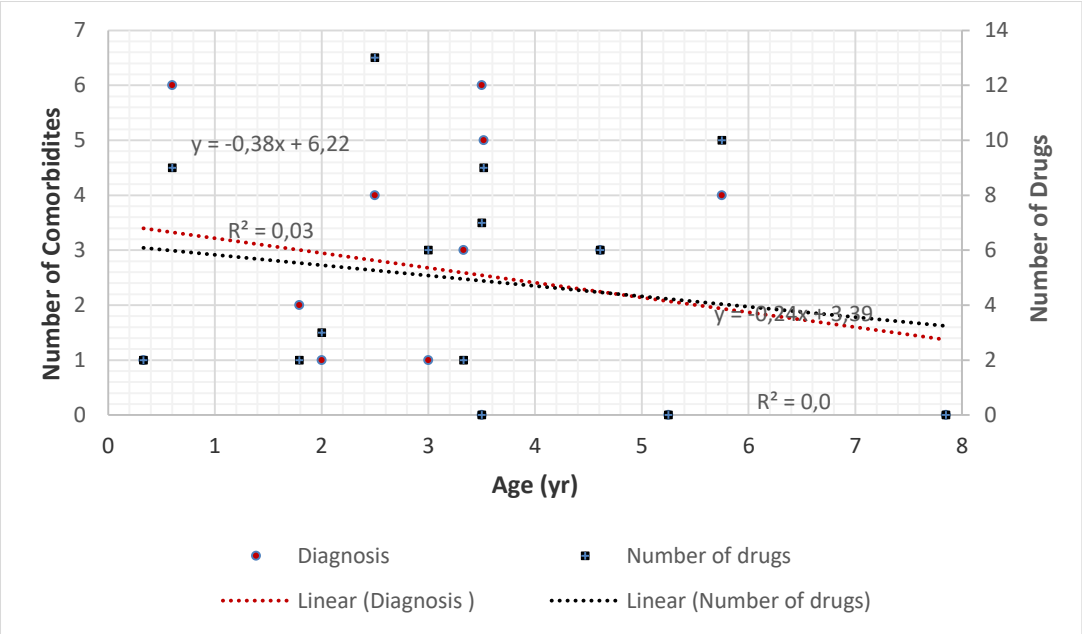

Figure 2 Correlation between drugs and comorbidities in relation to patient age.

DISCUSSION

This study showed that male patients aged 12 years and younger were more than the female patients. Gender differences indicating the predominance of male patients in the incidence of paediatric diseases have been reported in a number of studies [16][17][18][19]. The difference could be due to the gender distribution report of 2017 national population census in which male children aged from birth to 14 years old were more than 50% as compared to the female children of the same age group [7]. A study by Eleanor N. [20] reported that higher morbidity observed in males could be as a result of higher susceptibility to infectious diseases as females possess stronger humoral and cellular immune responses to infection or antigenic stimulation. Additionally, Ginsburg and Miller [21] showed that male children demonstrated more risk behaviours which explained the increased hospital visits seen in male patients. Furthermore, a study by Patil et al. [22] on prescription pattern monitoring reported the predominance

of male patients due to cultural practices where less number of girls visited the hospital for medical attention.

Majority of the patients in this study (37%) were infants (1 month – 1 year). This was in line with other similar studies by Nduka et al. [23] and Akhtar et al. [24] which reported 37.20% and 29.80% respectively. The increased susceptibility of this age group may be due to a number of reasons. Firstly, during the first few months of infancy, cells that allow essential bacteria to safely colonize the intestines of infants also suppress their immune systems making them more vulnerable to infections [25]. Secondly, cessation of breastfeeding in breastfed infants has been associated with acute morbidity events and negative health effects [26]. Thirdly, children aged 2 years and younger who attend childcare and preschool programs are usually exposed to greater risk of illness as they shift to new environments and increased contact with other children [27].

Overall, a total of 845 drugs comprised of 29 drug groups were identified in this study, in which antibiotics (18.34%) were the most commonly prescribed drug groups. The percentage of encounters with antibiotics was 35.47. According to the WHO, 15 – 25 % of prescriptions with antibiotics is expected in most developing countries where infectious diseases are more prevalent [28]. Our result was relatively high in comparison to the findings of similar studies conducted in other developing countries such as India (24.15%) [29] and Tanzania (33.70%) [30]. In contrast to our findings, studies from Nigeria (71.10%) [31] and Sierra Leone (74.80%) [16] reported higher results. However, most countries have reported relatively higher values than WHO. There are several factors influencing the prescribing of antibiotics in children, namely: (i) perceived demand or expectations from parents [32][33] (ii) diagnostic uncertainty as most patients with viral and bacterial infections often have similar symptoms [34] (iii) time constraints and workload as physicians can be pressured while formulating treatment plans [35].

The most frequently prescribed drug item in this study was Paracetamol (18.61%). Similar studies from across the globe have also reported high prescribing of Paracetamol, particularly in India (36.80%) [18], United Arab Emirates (87.50%) [36] and Gambia (88.80%) [37]. This frequent use may be due to the fact that children are most likely to experience fever and acute pain as a result of illness or injury [38]. The high frequency of prescribing Paracetamol was associated with age, notably in neonates and infants aged less than one year in comparison to older children ($p=0.17$). The availability of Paracetamol in different dosage forms, such as suppositories and oral preparations especially syrups and drops, makes it a drug of choice for neonates and infants as it aids in ease of administration [39]. Moreover, unlike most analgesics, Paracetamol is a licensed first line drug approved for use in neonates and infants and regarded less likely to cause ADRs and acute liver failure [40].

Average number of drugs per prescription is an important index in prescription monitoring [41]. The average number of drugs per prescription in this study was 2.58, which was higher than the results obtained from India (1.90) [18], Italy (1.40) [42] and Gambia (2.20) [37]. However, the average number in this study was lower compared to other similar studies from Sierra Leone (3.77) [16], France (2.80) [43], Saudi Arabia (3.0) [44] and Ghana (4.80) [45].

In general, the average number of drugs in the studies reported above is relatively higher than the recommended WHO average of 1.6 - 1.8 drugs per prescription [46]. It has been suggested that the optimal indicator values for the average number of drugs largely depend on disease patterns, policies and treatment guidelines and therefore may vary from country to country and over time [47]. However, the factors contributing to higher number of drug prescribing include the unavailability of clinical treatment guidelines, lack of prescribers' familiarity with treatment guidelines as well as the lack of recurrent medical training and education of the prescribers [35][48].

The various routes that were prescribed for drug administration were assessed. More than half of the drugs prescribed (62.96 %) were for oral routes, while parenteral routes (<1 %) were least prescribed. The low proportion of parenteral use observed may be as a result of the hospital outpatient setting in which the study was carried out. Generally, in outpatient department fairly stable patients are seen and followed up routinely, thus the need for injections is usually minimal. This practice is in line with rational drug use, as injudicious use of parenteral routes in not recommended when oral formulations are more appropriate, especially in the case of paediatric patients [49].

Of the total 419 disease conditions assessed, skin infections (35.56%) were most predominant, which was found to be similar to other studies [50][51][52]. The most common skin infection in this study was eczema (30.60%). Interestingly, this was in line with studies conducted by Katibi et al. [53] and Dlova et al. [54] carried out in KwaZulu-Natal, South Africa reporting a high frequency of eczema, (67.8%) and (51.8%) respectively in paediatric patients, suggesting that eczema is more common in this population. This high occurrence can be attributed to the fact that eczema has been described as common manifestations of Human Immunodeficiency Virus (HIV) infection in children [55]. A report by Dorrington et al. showed the prevalence of HIV in children aged 0-14 was highest in KwaZulu-Natal (33.25%) when compared to the other provinces in South Africa [56]. Skin diseases can also occur as a result of low socioeconomic status, poor hygiene and unfavourable tropical weather [57][58].

Of the 134 most common disease conditions analysed, the majority (74.63%) did not have comorbidities, while 25.37% had conditions ranging from 2 - 4 diseases. A negative correlation was observed between patient age and number of comorbidities (r = -0.24), where the number of comorbidities was 3.4 in neonates and infants within one year of age and 1.4 in children aged 8 years. A study by Gupta et al. [59] revealed higher disease conditions of 4.8 in infants aged less than 1 year old compared to 4.6 in children aged 5 years old. Similarly, a study by Marimuthu et al. [60] also reported a decrease in the prevalence of morbidity with increasing age, with 18.90% in infants aged less than 1 year and 10.70% in 9 years old children. The decrease in disease conditions with increasing age may be due to reasons such as (i) neonates and infants possess an immune system which is less developed compared to the older children [61], (ii) the antibodies transferred from mother to foetus during pregnancy which contribute to early defence against pathogenic organisms is short lived and decay within 6 months of age rendering infants susceptible to various diseases [62] (iii) maternal infections occurring in the third trimester are strongly associated with increased susceptibility of infants to parasitic infections [63].

CONCLUSION

This study reported on drugs prescribing patterns in an outpatient paediatric department at a tertiary care hospital in the province of Kwa-Zulu Natal, South Africa. The highest disease condition diagnosed was eczema and it was matched by the high prescription of emollient. There was a high antibiotic prescribing pattern among the paediatric outpatients, and penicillin was most often prescribed. The average number of drugs per prescription was higher than the World Health Organization's recommendation. The high extent of non-generic prescribing and substantial deviation from EML impedes the practice of rational drug use. Education and training of prescribers to promote rational drug prescribing, especially regarding generic prescribing is of utmost importance. Further, prescription pattern monitoring and evaluations using inpatients and other provincial health facilities are recommended to promote appropriate use of drugs and ensure patients safety.

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CHAPTER 4
SECOND MANUSCRIPT SUBMITTED FOR PUBLICATION

4.1 Introduction

This chapter describes the general findings and discussion of the study and is represented in the form of a manuscript titled “Compliance to Standard Treatment Guidelines and Essential Medicine List in Paediatric Outpatients at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa.”. This manuscript has been submitted to the *“African Journal of Primary Health Care & Family Medicine”* for publication.

4.2 Manuscript two

Compliance with Standard Treatment Guidelines and Essential Medicine List in Paediatric Outpatients at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa.

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ABSTRACT

Background: The South African paediatric standard treatment guidelines (STGs) and essential medicines list (EML) were initially introduced in 1998 with the aim of addressing most common disease conditions affecting the paediatric population. Data regarding the extent of compliance with treatment guidelines for paediatric patients in South Africa is limited.

Aim: This study aimed to evaluate the level of compliance of prescribed treatments at an outpatient paediatric department with reference to the South African 2017 paediatric STGs and to analyse the extent of drugs prescribed from the EML.

Setting: The study was conducted at a public sector tertiary hospital situated in KwaZulu-Natal, South Africa.

Methods: A descriptive, retrospective study based on data extracted from patient files and evaluated for compliance with the 2017 paediatric STGs/EML recommendations using the loose criteria model.

Results: Overall, 79.64% of the treatments prescribed were in accordance with the 2017 paediatric STGs. Treatments prescribed for tuberculosis 7/7 (100%), eczema 36/41 (87.80%) and tinea capitis 11/13 (84.62%) were most compliant with the guideline. The most commonly diagnosed disease conditions were skin infections 97/275 (35.27%), respiratory tract infections 59/275 (21.45%) and gastrointestinal diseases 37/275 (13.45%). Out of 845 drugs analysed, 354 (41.89%) were generic drugs prescribed from the EML while 491 (58.11%) were non-generic drugs prescribed under trade names.

Conclusions: Although majority of the treatments prescribed conformed with the South African 2017 paediatric STG recommendations, the extent of generic prescribing was low. There is a need to improve prescribing from EML by generic name.

Keywords: Paediatrics, compliance, generic drugs, Standard Treatment Guideline (STGs), Essential Medicine List (EML), South Africa.

BACKGROUND

The use of drugs is one of the most effective therapeutic interventions in health care, especially when utilized rationally [1]. Medicine use is considered rational when patients receive appropriate medicines, in doses that meet their individual requirements, for an adequate period of time and at the lowest cost both to them and the community [2]. This is vital in achieving quality medical care and delivering economic benefits to the individual and society. Nonetheless, irrational use of drugs remains a major issue facing most health systems across the world [3]. The World health organization (WHO) estimates that more than half of all drugs are inappropriately prescribed, dispensed, or sold, while approximately 50% of patients fail to take medication correctly [4].

Irrational use of drugs is a common feature of health care settings of most developing countries [5]. Irrational drug use can be described as the medically inappropriate and economically ineffective use of pharmaceuticals [6]. It can be manifested by failure to prescribe according to guidelines, prescribing drugs when no drug therapy is indicated, prescribing with incorrect dosage, administration or duration and prescribing unnecessarily expensive drugs [7]. Treatment guidelines are reportedly effective in remedying irrational drug use by providing consensus on most effective and economical treatment therapies available, maintaining consistency in treatment selection thereby reducing confusion among prescribers, reducing adverse drug reactions (ADRs) and other drug related complications; and can be used as tools to supervise, monitor and evaluate health care practices [8] [9].

Standard Treatment Guidelines (STGs) are systematically developed statements comprising a list of preferred pharmaceutical and non-pharmaceutical treatments for common health problems designed to assist prescribers in making appropriate decisions for specific clinical circumstances [8]. STGs incorporate a list of essential medicines as an extension of treatment regimens. Essential medicines are those that satisfy the priority health needs of a population, selected with due regard to the public health relevance as well as the safety, efficacy and cost-effectiveness of the product [10]. The concept of EML is based on the notion that using a limited number of well-known and cost-effective drugs can lead to better health care quality, enhanced supply and equitable access to products [11]. Application of STGs/EML is a necessity for developing countries like South Africa, where majority of the population depends on public health services with limited resources available.

The South African National Drug Policy (NDP) was initially adopted in 1996 with the goal of ensuring adequate and reliable supply of safe, cost-effective drugs of acceptable quality to all citizens [12]. This was subsequently followed by the implementation of the paediatric STGs/EML in 1998 [13]. Currently,

the 2017 paediatric treatment guidelines has been updated to its fourth edition and is has been implemented in all nine provinces where it is used to treat the common disease conditions [14].

According to the WHO, prescribing practices should be evaluated periodically in order to identify the magnitude of irrational drug use and explore appropriate and feasible strategies, which in turn increases quality of drug therapy, lowers ADRs and reduces wastage of resources [15]. Additionally, the NDP states one of the objectives for appropriate prescribing is to ensure that all drugs are prescribed in accordance with STGs/EML recommendations [12]. However, currently there is paucity of data regarding evaluation of treatment compliance studies, particularly in the paediatric population. This study therefore was undertaken at an outpatient paediatric department in a public sector tertiary hospital situated in KwaZulu-Natal, South Africa with the aim to evaluate the level of compliance of prescribed drugs in reference with the South African 2017 paediatric STGs and to analyse the extent of drugs prescribed from the EML.

METHODS

Study design and setting

This was a retrospective descriptive study, based on systematic sampling of paediatric patient files visiting the outpatient department. The study was conducted at a tertiary care hospital situated in Kwazulu-Natal, South Africa with the aim of evaluating the level of compliance of treatments prescribed for the indicated diagnoses in reference with reference the South African 2017 paediatric STGs, and to analyse the extent of drugs prescribed from the EML. Compliance was assessed using the loose criteria model, a method adopted from a report by the Ministry of Health and Social Services of Namibia and Systems for Improved Access to Pharmaceuticals and Services (SIAPS). The loose criteria model used in the assessment indicated that "drugs were prescribed as per the guidelines, but with the use of some additional drugs (vitamins and analgesics) or, alternatively, the treatment was not exactly as the STGs dictate, with some variation in dosing and administration" [16]

Study population and sampling

Paediatric outpatient files containing prescriptions dated between June 1, 2016 and May 30, 2017 were included. Patients aged 12 years and younger who attended the outpatient department, for whom prescriptions were written for were included in the study. A systematic sampling technique was used to minimize bias in the selection process and to ensure equal representation of samples. In total 419 disease conditions were assessed during the study period between November 18 - December 28, 2017. Disease

conditions that were not listed in the South African 2017 paediatric STGs were excluded, resulting in 275 disease conditions.

Data analysis

Data regarding the disease condition and diagnosis, patient demographic characteristics (age, gender and weight) as well as details of the prescribed treatments (drug name, dose, dosage form, frequency and duration of treatment) were extracted from the patient files. Based on the loose criteria model used in this study, prescribed treatments were considered to be compliant with the 2017 paediatric STGs/EML: (i) if the appropriate treatment was prescribed for the appropriate disease condition using correct treatment frequency and duration, alternatively with some variation in dosing or administration and: (ii) if the primary treatment was prescribed with additional symptomatic treatments such as vitamins and mineral (Figure 1).

Continuous variables such as age were summarized using mean ± standard deviation (SD), median and interquartile range (IQR) and composed using Wilcoxon-Mann-Whitney test Categorical variables such as gender were expressed as percentages (proportions) and composed using Chi-square test or Fisher's exact test as appropriate. A multivariate logistic regression test was used to determine the relationship between patient demographic characteristics and the likelihood of treatment compliance with STGs. A linear scatter plot based on regression analysis was generated using an independent t-test to compare the mean age of compliant patients with the mean age of non-compliant patients. All analyses were conducted using Statistical Package for Social Sciences® (SPSS®) version 25, and Minitab® version 12. All levels of significance were kept at 0.05.

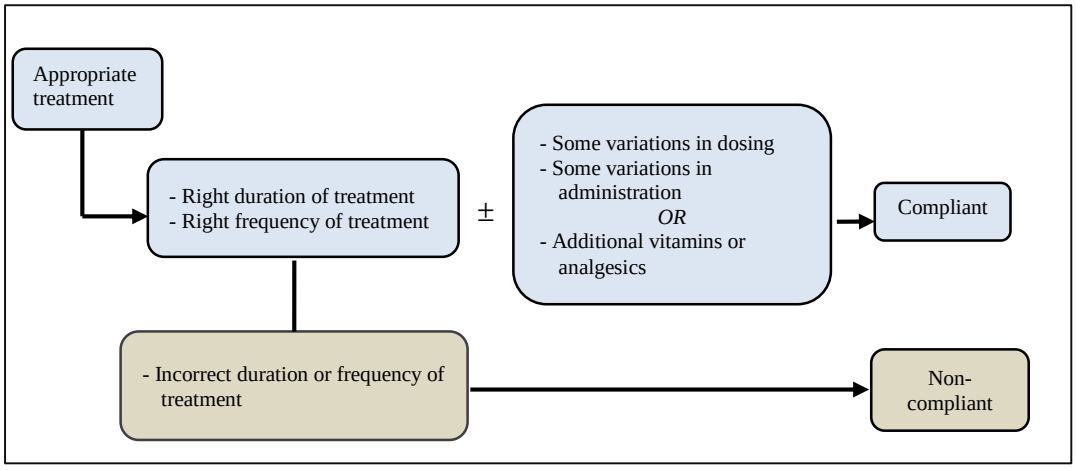

Figure 1 Flow diagram describing the loose criteria model used in this study for determining compliance with the 2017 paediatric STGs.

Ethical statement

Ethical approval was obtained from the Biomedical Research Ethics Committee, University of KwaZulu-Natal (BREC Ref: BE492/17). This study was registered on the South African National Health Research Database (NHRD) (Ref: KZ_201710_023). The KwaZulu-Natal Department of Health (DoH), Health Research and Knowledge Management also gave approval (HRKM Ref: 422/17) for the study. Permission to access patient files was obtained from the hospital administration KE 2/7/1 (46/2017).

RESULTS

Demographic characteristics of patients

From the 327 patient files reviewed, a total of 419 disease conditions were identified and assessed in this study. Disease conditions which were not listed in the 2017 paediatric STGs were excluded, resulting in 275. Out of the 275 disease conditions reviewed, 163 (59.27%) were for male patients and 112 (40.73%) for female patients. The age of patients ranged between 3 weeks and 12 years. The average age of patients was 3.02 ± 3.08 with median age 1.75 (IQR 4.33). The average age of males was 3.02 ± 3.08 and 3.04 ± 3.08 for female patients. Using the Kolmogorov-Smirnov® test for normality, age distribution was found to be non-normal (p value 0.000).

Study patients were categorized into 12 age groups ranging from birth to 12 years with an equal age interval of 1 year. Accordingly, majority of the conditions, 103/275 (37.45%) were found in patients in age group 1, followed by age groups 2 and 4, composed of 64/275 (23.27%) and 26/275 (9.45%) respectively. The weight of patients ranged between 3kg and 42.95kg, with majority 109/275 (39.64%) of the patients weighing 12 kg and less.

Compliance with the South African 2017 paediatric STGs

Overall, out of the 275 disease conditions assessed, treatments prescribed for 219 (79.64%) disease conditions were in accordance with the South African 2017 paediatric STGs, while treatments prescribed for 56 (20.36%) disease conditions did not comply with the guideline. Of the 219 compliant treatments, 130 (59.36%) were for male patients and 89 (40.64%) for female patients, whereas of the 56 non-compliant treatments, 33 (58.93%) were for male and 23 (41.07%) for female patients. In order

to determine a possible association between compliant treatments prescribed and patient demographic characteristics namely age, gender and weight, a Chi-square test was used which indicated that there were no statistically significant associations between compliance and the specified patient variables (Table 1).

Table 1 Chi-square test used to determine associations between compliant treatments and patient characteristics.

Variables		**Disease conditions with compliant treatments (N=219)**	**Chi-square**	**P-value**
Age	**≤ 2years**	136	1.102	0.294
	> 2years	83		
Gender	**Male**	130	0.34	0.854
	Female	89		
Weight	**≤ 12kg**	85	0.06	0.956
	> 12kg	80		

Additionally, a multivariate logistic regression model was used to predict the likelihood of compliance with STGs and patient demographic characteristics (age, gender and weight). In order to generate Odds Ratio (OR) two broad groups for age and weight were created:

- Group 1 = Patients aged ≤ 2 years and weight ≤ 12kg.
- Group 2 = Patients aged >2 – 12 years and weight > 12kg – 42.95kg.

Results from the logistic regression revealed that OR for patients in age group 1 was 0.876, Confidence Interval 95 % (CI) = 0.67 – 1.139, while OR for age group 2 was 1.205, CI = 0.861 – 1.685. This implies that there was a 20.50% increased likelihood for patients within group 2 to have been prescribed treatments that were compliant with STGs in comparison to patients in age group 1. Additionally, the OR for patients in weight group 1 was 1.009, CI = 0.734 – 1.387, while OR for patients in weight group 2 was 0.990, CI = 0.700 – 1.401. This implies there was a 9.0% increased likelihood for patients in weight group 1 to have been prescribed treatments that were compliant with STGs when compared to patients in weight group 2. However, since the 95% CI of 0.861 – 1.685 for age group 2 and 95% CI of 0.734 – 1.387 for weight group 1 spans less than 1.0, the increased odds did not reach statistical significance. (Table 2).

Table 2 Odds ratio (OR) and Confidence Interval (CI) estimates based patient characteristics.

Variables		Odds Ratio (OR)	Confidence Interval (CI) (95%)	
			Lower	Upper
Age	Group 1 (≤ 2years)	0.876	0.67	1.139
	Group 2 (> 2years)	1.205	0.861	1.685
Gender	Male	0.977	0.762	1.214
	Female	1.034	0.728	1.468
Weight	Group 1 (≤ 12kg)	1.009	0.734	1.387
	Group 2 (> 12kg)	0.990	0.700	1.401

Compliance with the South African 2017 paediatric STGs by disease group

In order to determine the level of compliance by disease groups, individual disease conditions were categorized according to the organ systems and international classification of disease (ICD-10) system used in the 2017 South African paediatric STGs. Accordingly, the most predominant disease groups were skin infections 97/275 (35.27%), respiratory tract infections 59/275 (21.45%) and gastrointestinal diseases 37/275 (13.45%). Neonatal conditions and blood disorders were the least common disease groups, 2/275 (0.73%) and 4/275 (1.45%) respectively.

In terms of compliance, treatments prescribed for tuberculosis 7/7 (100%) were most compliant, followed by gastrointestinal disorders 33/37 (89.19%) and respiratory infections 52/59 (88.14%). Treatments prescribed for emergency and trauma 1/5 (20.0%) and eye conditions 2/6 (33.33%) were least compliant with STGs (Table 3).

Table 3 Frequency distribution of disease groups and level of compliance with the 2017 paediatric STGs.

Disease group	Disease conditions assessed n, (%)	Compliance with STGs	
		Complaint n, (%)	Non-complaint n, (%)
Skin infections	97 (35.27%)	76, (78.35%)	21 (21.65%)
Respiratory infections	59 (21.45%)	52 (88.14%)	7 (11.86%)
Gastrointestinal	37 (13.45%)	33 (89.19%)	4 (10.81%)
Ear, nose, throat	29 (10.55)	21 (72.41%)	8 (27.59%)
Nervous system	14 (5.09%)	12 (85.71%)	2 (14.29%)
Infectious diseases	9 (3.27%)	7 (77.78%)	2 (22.22%)
Tuberculosis	7 (2.55%)	7 (100%)	-
Eye conditions	6 (2.18%)	2 (33.33%)	4 (66.67%)
Nephrological/Urological disorders	6 (2.18%)	4 (66.67%)	2 (33.33%)
Emergency and trauma	5 (1.82%)	1 (20.00%)	4 (80.00%)
Blood disorders	4 (1.45%)	3 (75.00%)	1 (25.00%)
Neonatal conditions	2 (0.73%)	1 (50.00%)	1 (50.00%)
Total	**275 (100%)**	219	56

Compliance with the South African 2017 paediatric STGs by individual disease conditions

Extent of compliance by individual disease conditions were also assessed in this study. For purpose of this assessment the most common diseases with a diagnoses frequency of 5 and above were analysed. Accordingly, all treatments prescribed for tuberculosis 7/7 (100%) were found to be in line with the South African 2017 paediatric STG recommendations, followed by treatments prescribed for eczema 36/41 (87.80%) and tinea capitis 11/13 (84.62%). Treatments prescribed for impetigo 2/10 (20%) and rhinitis 2/6 (33.33%) were least compliant with STGs. The extent of compliance by disease conditions is shown in Table 4.

Table 4 Extent of compliance with 2017 paediatric STGs by disease conditions.

Disease conditions	Number of diseases assessed	Number of STGs compliant treatments prescribed	Percentage compliance with STGs
TB	7	7	100.00
Eczema	41	36	87.80
Tinea capitis	13	11	84.62
Epiglottitis	6	5	83.33
Acute GE	17	14	82.35
Laryngotracheobronchitis	5	4	80.00
Seizures	7	5	71.43
Tonsillitis	12	8	66.67
Pneumonia	6	4	66.67
Asthma	6	4	66.67
Bronchopneumonia	5	3	60.00
Bronchitis	12	7	58.33
Rhinitis	6	2	33.33
Impetigo	10	2	20.00

Overall, the total number of drugs prescribed in this study was 845, of which 354 (41.89%) were generic drugs prescribed from the 2017 paediatric EML and 491 (58.11%) non-generic drugs prescribed under trade names which were not listed in the EML. The 845 drugs assessed were constituted by 29 drug groups based on their therapeutic use, of which antibiotics 155/845 (18.34%) were the most predominantly prescribed, followed by emollients 118/845 (13.96%), analgesics 117/845 (13.85%) and corticosteroids 98/845 (11.60%). The least prescribed drug groups included antiprotozoal 1/845 (0.12%), antihypertensive 1/845 (0.12%), topical antiviral 1/845 (0.12%), anaesthetics 2/845 (0.24%) and diuretics 3/845 (0.35%).

Table 5 depicts the extent of compliance of the most commonly prescribed drug groups and individual drugs with the 2017 paediatric EML. All antimyotics 19/19 (100%) and antimycobacterials 7/7 (100%) were prescribed from the EML and had the highest level of generic prescribing, followed by zinc supplements 11/12 (91.67%), emollients 108/118 (91.53%) and vitamins 17/27 (62.96%). The lowest proportion of drugs prescribed from the EML included decongestants 0/33 (0%) sodium supplements 0/25 (0%) and antipsoriatics 0/13 (0%) in which all drugs were prescribed under trade names, followed by antihistamines 10/97 (10.31%), antibiotics 24/155 (15.48%) and bronchodilators 3/17 (17.65%).

Table 5 Extent of compliance with 2017 paediatric EML by drug groups and individual drugs.

Drug group	Individual generic drugs (listed in EML)		n, (%)	Individual non-generic drugs (unlisted in EML)		n, (%)
Antimycobacterials	Isoniazid+ Rifampicin	n=7	7, (100%)	-		-
Antimyotics	Fluconazole	n=19	19, (100%)	-		-
Emollients	Aqueous cream	n=63	108, (91.53%)	Aracus cream®	n=5	10, (8.47 %)
				Aldara cream ®	n=3	
	Emollient cream	n=26		Barrs ointment®	n=1	
	Emulsifying ointment	n=14		Canesten cream®	n=1	
	Castor oil + zinc	n=5				
Zinc supplements	Zinc sulphate	n=11	11, (91.67%)	Zinplex®	n=1	1, (8.33%)
Decongestants	-	-	-	Illadin nose drop®	n=5	33, (100%)
				Saline nose drop	n-28	
Corticosteroids	1% Hydrocortisone	n=23	57, (58.16%)	Procutan cream®	n=14	41, (41.84%)
	Prednisone	n=10		Cortoderm®	n=9	
	Bethametasone cream	n=8		Fluticasone nasal spary®	n=9	
				Dovate cream®	n=9	
	0.03% Bethametasone	n=14				
	Methylprednisolone	n=2				
Vitamins	Multivitamin	n=9	17, (62.96%)	Vi-Dalyin®	n=7	10, (37.04%)
	Vitamin D	n=8		Retin A®	n=3	
Antianaemics	Ferrous sulphate	n=6	12, (54.55%)	Folate®	n=10	10, (45.45%)
	Ferrous gluconate	n=5				
	Essential iron	n=1				
Antibiotics	Cephalexin	n=10	24, (15.48%)	Amoxil®	n=51	131, (84.52%)
	Amoxicillin	n=4		Augmentin®	n=40	
	Ciprofloxacin	n=3		Cefril®	n=27	
	Clarithromycin	n=2		Flamazine cream®	n=7	
	Cloxacillin	n=2		Fusidic acid eye ointment®	n=6	
	Doxycycline	n=1				
	Flucloxacillin	n=2				

Table 5 (continued).

Drug group	Individual generic drugs (listed in EML)		n, (%)	Individual non-generic drugs (unlisted in EML)		n, (%)
Analgesics	Paracetamol	n=32	38, (32.48%)	Panado®	n=78	79, (67.52%)
				Bideflan®	n=1	
	Ibuprofen	n=6				
Bronchodilators	Sodium valporate	n=1	3, (17.65%)	Asthavent®	n=6	14, (82.35%)
	Budesonide	n=1				
	Sulbutamol	n=1		Neulin®	n=8	
Sodium Supplement	-	-	-	Sorol®	n=21	25, (100%)
				Mist pot chlor	n=4	
Antihistamine	Cetrizine	n=10	10, (10.31%)	CTM®	n=45	87, (89.69%)
				Allergex syrup®	n=33	
				Allergex®	n=9	
Antipsoriatic	-	-	-	Epizone A cream®	n=7	13, (100%)
				LPC shampoo®	n=6	

In order to determine whether there was an association between patient age and compliance with STGs for whom generic drugs were prescribed for, we selected the most common generic drugs that had a prescribing frequency of 10 and above. Using an independent t-test we compared the mean age of patients that received compliant treatments against patients with non-compliant treatments for the selected drugs. Overall, it was observed that compliance was higher in older patients (mean age= 2.29 ± 2.44 years), with the exception of patients prescribed with zinc sulphate, saline nose drops and 1% hydrocortisone, in which compliance was found to be higher for the younger patients (mean age = 0.67 ± 0.14 years). A statistically significant difference was also noted in the mean age of patients between compliant and non-compliant treatments for cetrizine ($p = 0.008$) and zinc sulphate ($p = 0.002$) as shown below in Figure 2.

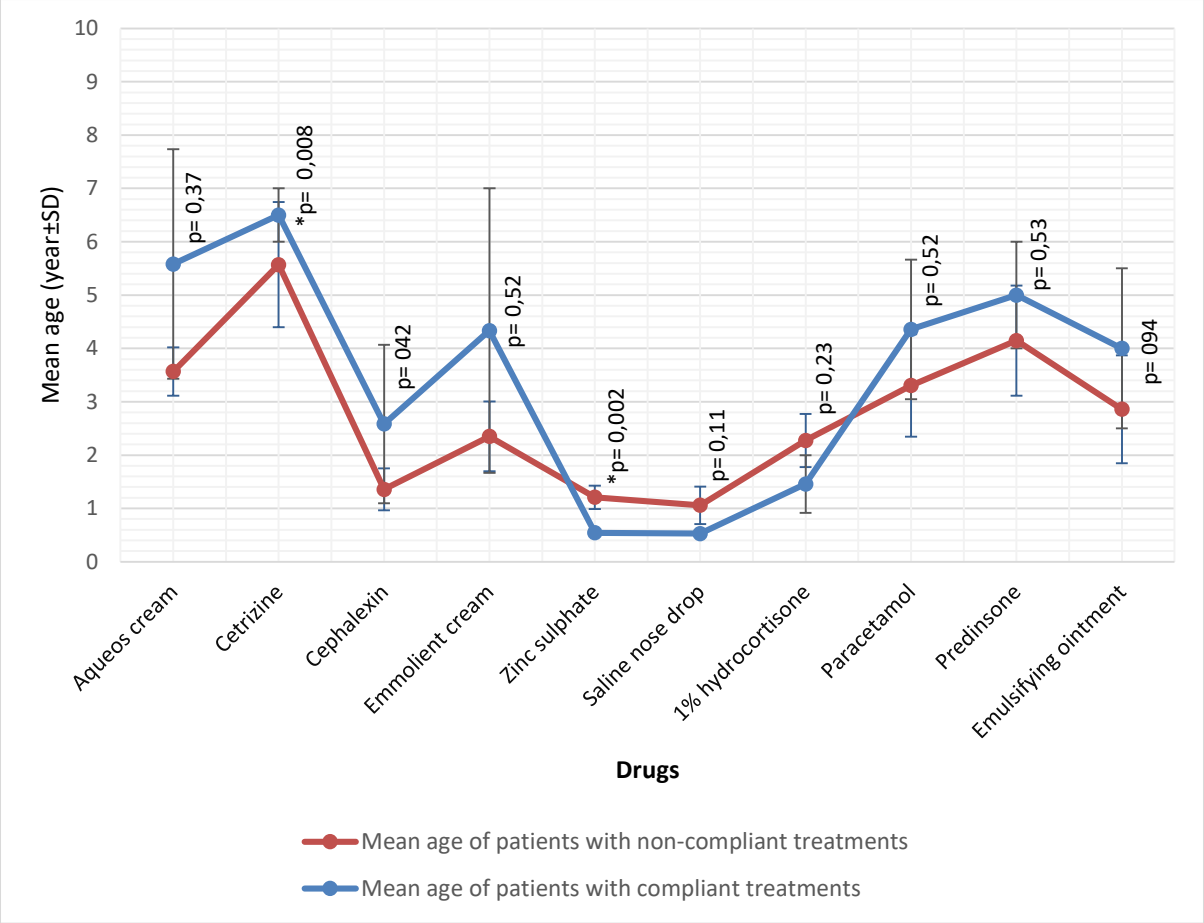

Figure 2 Linear scatter plot comparing patient mean age and compliance with 2017 paediatric STGs for the selected drugs.

*p - statistically significant

DISCUSSION

The goal of the South African STGs is to reduce variation in prescribing practices, guide the appropriateness of drug choice, and improve the quality of patient care across all public health facilities in the country [14]. In this study, the majority (79.64%) of the treatments prescribed were compliant with the 2017 South African paediatric STG recommendations. According to the Management Sciences for Health (MSH), STG compliance of more than 90% is desired whereas compliance of more than 85% is considered acceptable [17], therefore, compliance in this study can be considered as marginally optimal. Our result was somewhat lower in comparison to the study finding by Engelbrecht S. [18] conducted in adult patients which reported compliance at 89.90%, however compares fairly to the findings presented by Niaz Q. (71.90%) [19]. Contrary to the studies mentioned above, our findings were significantly higher compared to a similar study by Hlongwana S. carried out in paediatric patients in Umkhanyakude health district, KwaZulu Natal where only 38% of prescriptions complied with STGs [20].

This study assessed for possible correlations between patient demographic characteristics and compliant treatments prescribed using logistic regression models and Chi-square tests, which revealed there were no statistically significant associations between compliance and patient demographic characteristics ($p > 0.05$). However, in contrast to our findings, a study conducted by Afreen and Rahman reported a significant variation in compliance with STGs between younger patients (29.50%) and older patients (52.70%) [21]. Similarly, a study by Niaz Q. revealed compliance with STGs in older patients to be 72.80% in comparison to younger patients 66.81% [19]. These variation may be attributed to the fact that older children suffer from fewer morbidities and infections compared to younger children due to stimulation of protective responses from immunizations and vaccines [22].

In this study, skin infections were the most predominant disease group, similar to the results from other studies by Marrone et al. [23] and Sardana et al. [24]. A study by Dlova et al. assessing the spectrum of skin diseases in Durban, South Africa, revealed that the highest frequency of eczema (51.80%) was found in paediatric patients, suggesting that eczema is more prevalent in paediatric populations [25]. Skin infections affect 21 – 87 % of children in developing countries as a result of poor hygiene and low socioeconomic status [26]. The high occurrence of skin infections could also be attributed to the under developed immune system present in children which may affecting the protective ability of the skin as well as pose greater susceptibility to various allergic reactions [27].

Respiratory tract infections were the second most prevalent disease groups evaluated in this study. This was in agreement to a study undertaken at a paediatric hospital in Cape Town, South Africa which reported respiratory tract infections were the second most common cause for hospital visits [28]. These results coincide with the data report from the Statistics South Africa (SSA), which classified respiratory disorders among one of the leading cause of morbidity in children aged 14 and younger [29]. Furthermore, study findings by Worku Z. which show respiratory infections account for more than 50% of child morbidity in South Africa [30]. There are several predisposing factors contributing to high respiratory infections observed in children namely, low birth weight, lack of immunization, concomitant diseases such as asthma, exposure to polluted air, micronutrient deficiency and overcrowding during day care attendance [31].

Compliance with the 2017 paediatric STGs varied considerably according to the disease groups being treated. Full compliance was observed in tuberculosis (100%), where all drugs prescribed complied with the 2017 paediatric STG recommendations, hence meeting the 95% global target set by the WHO in the prevention management of tuberculosis [32]. Our results were comparable to the study findings by Ershova et al. carried out in three provinces of South Africa, revealing an overall compliance of 96.20% with STG recommendations for TB management [33]. Similarly, another study conducted in Cape Town, South Africa reported compliance for TB was 89.50% [34].

Gastrointestinal disorders (89.19%) had the second highest proportion of compliant treatments. Our findings were relatively lower in comparison to a study by Reddy K. carried out in KwaZulu-Natal, South Africa which reported 97% of the patients received appropriate treatments in the management gastrointestinal disorders [35], however was notably higher in comparison to a study by Cheraghali et al. conducted in Iran which reported 12% compliance rate [36]. According to statistical reports from the National Burden of Disease (NBD), gastrointestinal diseases account for 8.80% of infectious mortality in children aged 5 years and younger in South Africa [37]. This is largely linked to poor nutritional and environmental conditions, socio-economic status as well as existing comorbidities [38].

In this study, the least compliant treatments were prescribed for impetigo (20%). The most commonly prescribed drug that did not comply with STG recommendations in the management of impetigo was sulphur ointment. Sulphur ointment is a scabicidal agent which is usually used for the treatment of scabies [14]. Instead, the South African 2017 paediatric STGs recommends the use of topical antiseptics such as povidone iodine or oral antibiotics namely cephalexin and flucloxacillin. The frequent inappropriate prescribing of sulphur ointment may be due to the fact that impetigo often occurs secondary to scabies infection and usually characterised with similar signs and symptoms which could cause uncertainty in the diagnosis and treatment prescribing process.

Generic prescribing has been found to promote rational drug use, reduce drug cost and enhance better communication among healthcare providers [39]. The use of generic names ensures use of common terminologies between prescribers and dispensers in a health care facility, thereby reducing dispensing errors [16]. In this study, the overall rate of generic prescribing was 41.89 %, this is markedly lower than the standard value set by the WHO of 100 %. Our result was fairly comparable to the study findings carried out in the United States (40.60%) [40], Yemen (41.0%) [41] and Bangladesh (49.0%) [42], however much lower compared to findings from India (98.40%) [43], Ethiopia (97.50%) [44] and Gambia (74.80 %)[45]. Possible reasons for low generic prescribing could be prescribers doubt regarding the efficacy and bioavailability of generic formulations, poor knowledge of treatment guidelines, unawareness of the price variations between generic and branded drugs as well as the tendency of prescribers to avoid using lengthy names especially in combination drugs such as amoxicillin/clavulanic acid (Augmentin®), trimethoprim/sulfamethoxazole (Cotrim®) [7] [46]. Low prevalence of generic prescribing could also be attributed to lack of patients acceptance of generics which could be influenced by age, educational level, perceived seriousness of illness and limited awareness and information about generic drugs [47].

Limitations of the study

The study was conducted at one health facility and this prevents generalisation of the results to other health facilities in KwaZulu-Natal as well as the larger paediatric population in South Africa. Additionally, this was a descriptive study therefore, the underlying factors influencing the prescribing practices, especially with regards to low generic prescribing were not assessed.

CONCLUSION

This study showed majority of the treatments prescribed were in line with STG recommendations. The high rate of compliance observed in the management of tuberculosis and gastrointestinal disorders is encouraging, as both conditions are identified as major causes of childhood morbidities in developing countries. The low extent of generic prescribing and substantial deviation from EML however impedes the practise of rational drug use and suggests for managerial, regulatory and educational intervention strategies. Further explanatory studies are needed to probe the underlying factors and reasons influencing generic prescribing.

Acknowledgements

We wish to thank the hospital administration for granting us permission to carry out this study, the staff of medical record office and pharmacy department for their assistance and cooperation during data collection.

Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this paper.

Authors' contributions

Research idea and study design: Z.T, F.O and E.O; Data acquisition: Z.T; Statistical analysis: W.S; Supervision and Mentoring: F.O and E.O. Each author contributed important intellectual content during manuscript drafting and revision.

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CHAPTER 5
SYNTHESIS

5.1 Introduction

This chapter highlights the significant findings of the study, it gives a general conclusion drawn from the study, states the strengths and limitations and provides recommendations for future studies.

This study was carried out to monitor the prescription pattern in an outpatient paediatric department at a public sector tertiary hospital located in KwaZulu-Natal, South Africa and to assess the level of compliance with reference to the South African paediatric STGs. It also aimed to evaluate the extent of drugs prescribed from the EML. In order to achieve this, the following specific objectives were outlined:

- For which disease conditions, occurring in the paediatric population are drugs prescribed?
- What drugs are most often prescribed, according to therapeutic classes?
- To what extent are the prescribed drugs appropriate in the paediatrics according to STGs?
- To what extent are drugs prescribed from the EML?
- What is the average number of drugs per prescription for a patient?

5.2 Conclusions drawn from the study findings based on each of the objectives

Based on the WHO optimal number of drugs per prescription, the study findings showed a relatively higher value of 2.58 drugs per prescription in the outpatient paediatric department. Prescribing using non-generic drugs (58.11%) under trade names not listed in the EML was widely observed. The study found a high pattern of antibiotic prescribing (35.47%) among the paediatric patients, of which penicillin, penicillin combined with beta-lactamase inhibitors and cephalosporin were most often prescribed. The most commonly prescribed drugs according to therapeutic class following antibiotics were emollients, analgesics and corticosteroids. The high incidence of skin infections (35.56%), including eczema, scabies and tinea capitis which collectively accounted for more than half of all the identified skin conditions were the major factors driving the high prescribing of emollients and corticosteroids. The study concludes that majority (79.64%) of the treatments prescribed were compliant with the 2017 South African paediatric STG recommendations. The high rate of compliance observed in the management of tuberculosis and gastrointestinal disorders is encouraging, as both conditions are identified as major causes of childhood morbidities in developing countries.

5.3 Strengths of the study

- This study provides baseline information regarding the current trend in prescribing and the level of compliance with STGs/ EML in paediatric outpatients, a population group where paucity of data exists.
- Based on the findings of this study, key stakeholders will be able to plan targeted and informed interventions to overcome the identified drug use problems, and to direct resources where they would be most optimally utilised.

5.4 Limitations of the study

- The study was conducted at one health facility and this prevents generalisation of the results to other health facilities in KwaZulu-Natal as well as the larger paediatric population in South Africa. Further research is needed to study the prescription patterns and extent of compliance with treatment guidelines in paediatric patients at provincial level to reflect the national trend in drug usage and compliance rate.
- This was purely a descriptive study, thus the underlying reasons or factors influencing prescribing, especially with regards to low generic prescribing were not assessed.
- Prescriptions of paediatric inpatients were not monitored and evaluated.

5.5 Recommendations

- Provide frequent refresher workshops for prescribers; which will encourage them to make correct references of treatments for disease conditions and enhance compliance with existing guidelines.
- Increase the training and education of prescribers regarding use of EML, and ensue that the pharmaceutical supplies listed in the EML are available at all times so as to promote generic prescribing and other WHO prescribing indicators.
- Introduce compulsory rational drug use concept training in the orientation of newly appointed prescribers and interns to improve rational prescribing.

- Establish functional Pharmaceutical and Therapeutic Committees (PTCs) to encourage discussion on therapeutic issues including rational drug use and STGs compliance in order to curb any irrational practices in the health facility.
- Strengthen supervision of prescribers to ensure compliance with treatment guidelines.

- Employ further prescription pattern monitoring and evaluations that will focus on public and private health facilities.

- Conduct further explanatory studies to probe the underlying factors and reasons influencing generic prescribing and compliance.

5.6 Summary

In summary, this study has generated findings that can serve as a catalyst for future research in prescription pattern monitoring and evaluating compliance of prescribed treatments with the STGs/EML. The study can also help the stakeholders in revising the guidelines, and developing optimal strategies and interventions to overcome the current trend in irrational prescribing.

ANNEXURE 1

Ethical approval from the Biomedical Research Ethics Committee, University of KwaZulu-Natal.

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

15 November 2017

Mr ZB Tsegay (216076821)
Discipline of Pharmaceutical Science
School of Health Sciences
College of Health Sciences
fanielbeyene@yahoo.com

Dear Mr Tsegay

PROTOCOL: Prescription pattern monitoring of outpatient paediatric patients.
Degree: Masters in Pharmacy **BREC Ref No: BE492/17**

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 28 July 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 09 November 2017 to BREC correspondence dated 13 October 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 15 November 2017.

This approval is valid for one year from **15 November 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **12 December 2017.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Deputy Chair: Biomedical Research Ethics Committee

cc supervisor: posthuizenf@ukzn.ac.za
cc postgraduate administrator: nenepp1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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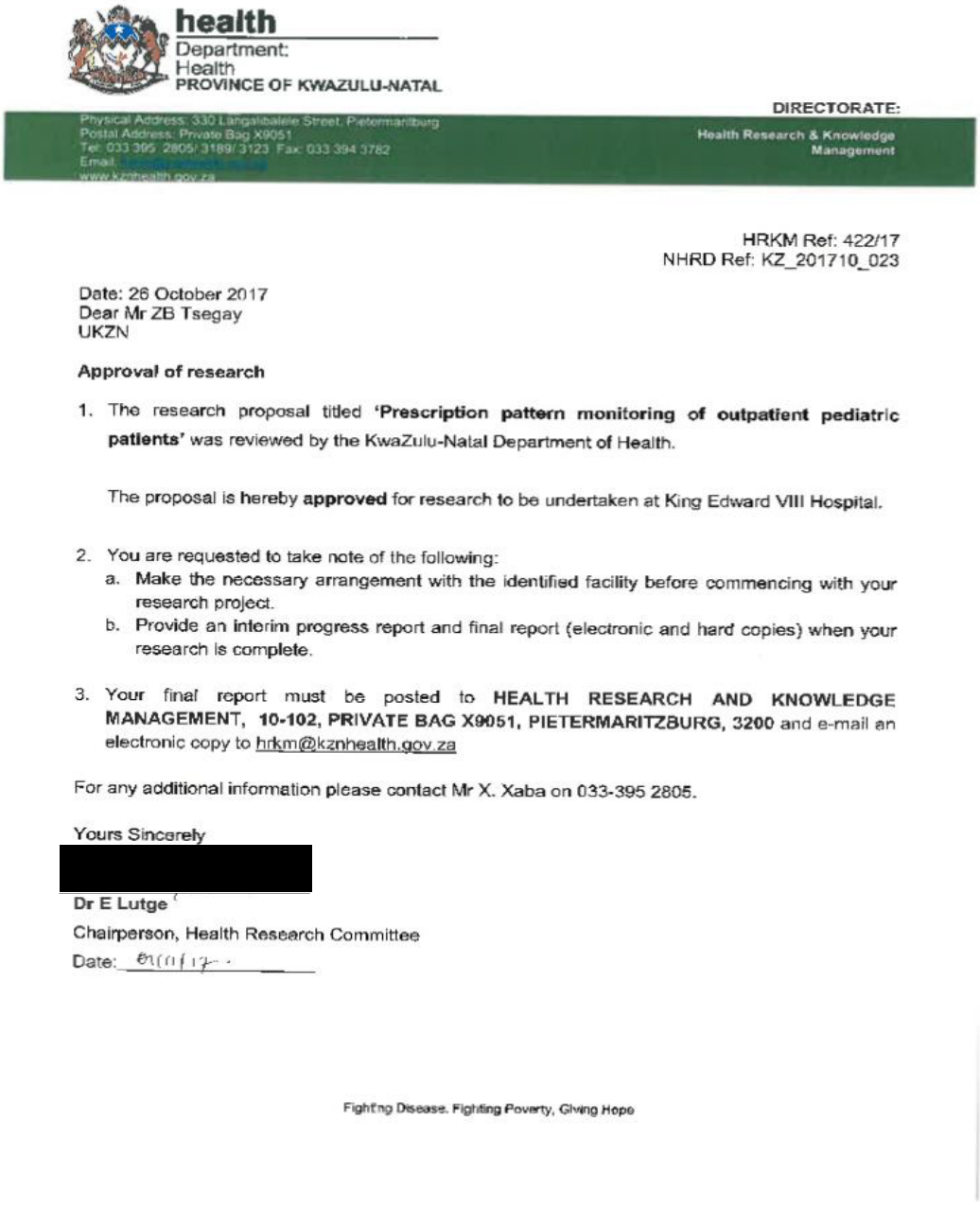
ANNEXURE 2

Approval of research from the South African National Health Research Database and Health Research and Knowledge Management.



health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

HRKM Ref: 422/17
NHRD Ref: KZ_201710_023

Date: 26 October 2017
Dear Mr ZB Tsegay
UKZN

Approval of research

1. The research proposal titled **'Prescription pattern monitoring of outpatient pediatric patients'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 26/10/17

Fighting Disease, Fighting Poverty, Giving Hope

ANNEXURE 3

Approval letter from the hospital administration to conduct research.

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO
KING EDWARD VIII HOSPITAL

Private Bag X02, CONGELLA, 4013
Corner of Rick Turner (Francois Road) & Sydney Road
Tel: 031-3603853, Fax:031-2061457, Email: [redacted]
www.kznhealth.gov.za

Ref.: KE 2/7/1/(46/2017
Enq.: Mrs. R. Sibiya
Research Programming

22 September 2017

Mr. ZB Tsegay
Discipline of Pharmaceutical Science
Westville Campus
UNIVERSITY OF KWAZULU-NATAL

Dear Mr. Tsegay

Protocol: "Prescription pattern monitoring of out-patient Paediatric Patients" Degree – Masters in Pharmacy; BREC REF. NO. BE492/17

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending receipt of approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following:-

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

[redacted]

SUPPORTED/NOT SUPPORTED

26/9/2017
DATE

DR. S. RAMJI
ACTING SENIOR MEDICAL MANAGER

ANNEXURE 4

Cover page for manuscript one submitted to the International Journal of Pediatrics and Adolescent Medicine.

Manuscript Details

Manuscript number	IJPAM_2019_65
Title	Prescribing Patterns in Paediatrics Outpatient Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa
Short title	Prescribing Patterns in Paediatrics Outpatients
Article type	Original article

Abstract

Background: Prescription Pattern Monitoring Studies are tools for assessing the prescribing and dispensing of drugs. They help in explaining the extent, trend and compliance of drug prescribing and play a vital role in promoting rational drug use. There is limited information on drug prescribing in the paediatric population in South Africa. The aim of this study was to evaluate the drug prescribing patterns in paediatric outpatients department at a tertiary care hospital in Kwa-Zulu Natal, South Africa. Methods: A descriptive, retrospective study was conducted at the paediatric outpatient department of a tertiary care hospital from November 18 - December 28, 2017. Patient demographics, diagnosis, and drugs prescribed were extracted from the patient files and captured using Microsoft Excel® 2016. Data was analyzed using Statistical Package for Social Sciences® version 25 and Minitab® version 18 statistical software. Results: A total of 327 patient files comprised of 193 (59.02%) male and 134 (40.98%) female patients were assessed. Majority of the patients were infants 121 (37%) within the age group of 1 month - 1 year. The average age of patients was 3.06 ± 3.21 years, interquartile range 4.33 years. Overall, 845 drugs were prescribed of which 354 (41.89%) were generic. The most frequently prescribed drug groups were antibiotics 155 (18.34%), emollients 118 (13.96%) and analgesics 117 (13.85%). Panado® 78 (13.20%) and aqueous cream 63 (10.66%) were amongst the most commonly prescribed drugs items. The percentage of encounters with antibiotics was 35.47% and average number of drugs per prescription was 2.58. The most encountered disease conditions were eczema, acute gastroenteritis, and scabies with frequencies of 41 (30.60%), 17 (12.69%) and 15 (11.19%) respectively. Conclusion: There was a high level of antibiotic prescribing pattern among the paediatric outpatients, and penicillin was the most often prescribed. The average number of drugs per prescription identified in this study was higher than that recommended by World Health Organization. The need for training of prescribers and healthcare professionals is of utmost importance in order to promote appropriate use of drugs and overall patient safety.

Keywords	Paediatric, prescription patterns, drugs, disease conditions, comorbidities.
Manuscript category	Original Article
Corresponding Author	Elizabeth Ojewole
Order of Authors	Zerisenay Tsegay, Elizabeth Ojewole, Wilbert Sibanda, Frasia Oosthuizen
Suggested reviewers	Suleiman El- Sharif, Nakul Gupta, Lita Thomas

Submission Files Included in this PDF

File Name [File Type]

Cover letter IJPAM 2019.pdf [Cover Letter]

Title Page Final.pdf [Title Page (with Author Details)]

Blind Manuscript- IJPAM FINAL.docx [Manuscript (without Author Details)]

Conflict of interest final.pdf [Conflict of Interest]

Ethical statement.pdf [Ethical Statement]

Authors Signatures.pdf [Author Agreement]

To view all the submission files, including those not included in the PDF, click on the manuscript title on your EVISE Homepage, then click 'Download zip file'.

ANNEXURE 5

Confirmation email from the International Journal of Pediatrics and Adolescent Medicine for manuscript submission.

Dear Mr Tsegay,

Submission no: IJPAM_2019_65
Submission title: Prescribing Patterns in Paediatrics Outpatient Department at a Tertiary Care Public Sector Hospital in KwaZulu-Natal, South Africa
Corresponding author: Dr Elizabeth Ojewole
Listed co-author(s): Dr Wilbert Sibanda, Mr Zerisenay Tsegay, Dr. Frasia Oosthuizen

Dr Ojewole has submitted a manuscript to International Journal of Pediatrics and Adolescent Medicine and listed you as a co-author. This email is to let you know we will be in contact with updates at each decision stage of the submission process.

The link below takes you to a webpage where you can sign in to our submission system using your existing Elsevier profile credentials or register to create a new profile. You will then have the opportunity to tailor these updates and view reviewer and editor comments once they become available.

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ANNEXURE 6

Confirmation email from the African Journal of Primary Health Care & Family Medicine and current status for manuscript.

Ref. No.: 2097
Manuscript title: Compliance with Standard Treatment Guidelines and
Essential Medicine List in Paediatric Outpatients at a Tertiary Care Public
Sector Hospital in KwaZulu-Natal, South Africa.
Journal: African Journal of Primary Health Care & Family Medicine
****
Dear Zeisenay Tsegay

Your submission has been received by the journal and will now be processed
in accordance with published timelines.

Processing time guidelines are available under the journal's 'About'
section, however, please note that each submission is assessed on its
individual merit and in certain circumstances processing times may differ.

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ANNEXURE 7

Data extraction tool

Title: Prescription pattern monitoring of outpatient pediatric patients.

Patient demographics			**Diagnosis and drugs prescribed**						**Compliance**	
Age	Sex	Wt.	Diagnosis	Drug name	Strength	Dose	Freq.	Tx duration	Compliant	Non-complaint

ANNEXURE 8

Submission guideline for International Journal of Pediatrics and Adolescent Medicine.

GUIDE FOR AUTHORS

Types of paper

Contributions falling into the following categories will be considered for publication: Original articles, review articles, case reports, invited instructive cases, images in pediatrics, quality of care in pediatrics, clinical practice guidelines, leadership articles, and What's your diagnosis.

Submission checklist

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Manuscript:
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Authorship
All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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This journal operates a double blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

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It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Subdivision - numbered sections
Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. (the abstract is not included in section numbering). Use this numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Introduction
State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Theory/calculation
A Theory section should extend, not repeat, the background to the article already dealt with in the Introduction and lay the foundation for further work. In contrast, a Calculation section represents a practical development from a theoretical basis.

Results
Results should be clear and concise.

Discussion
This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

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If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

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Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

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Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

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List funding sources in this standard way to facilitate compliance to funder's requirements:

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If no funding has been provided for the research, please include the following sentence:

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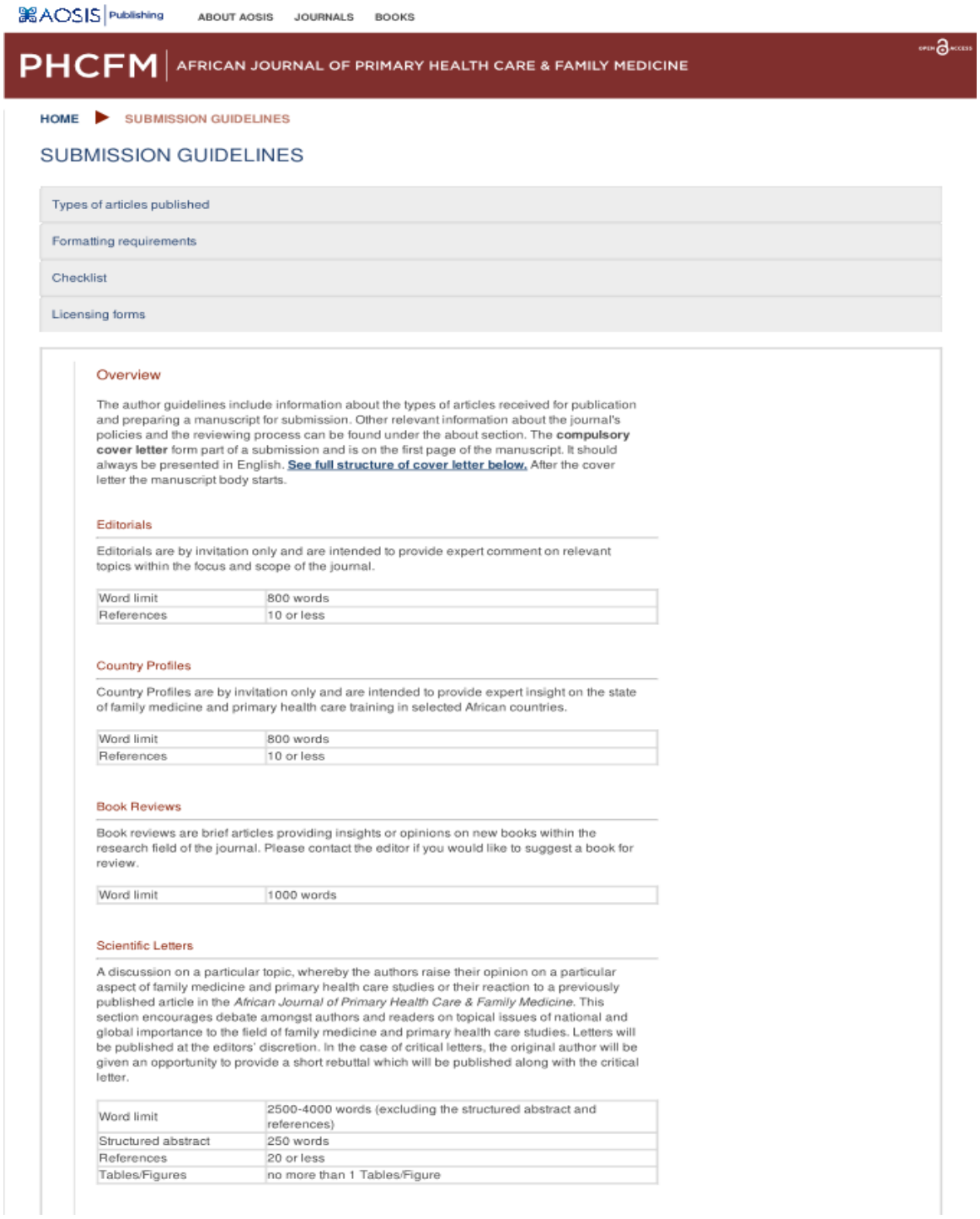
ANNEXURE 9

Submission guideline for African Journal of Primary Health Care & Family Medicine.



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SUBMISSION GUIDELINES

- Types of articles published
- Formatting requirements
- Checklist
- Licensing forms

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** form part of a submission and is on the first page of the manuscript. It should always be presented in English. **See full structure of cover letter below.** After the cover letter the manuscript body starts.

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Editorials are by invitation only and are intended to provide expert comment on relevant topics within the focus and scope of the journal.

Word limit	800 words
References	10 or less

Country Profiles

Country Profiles are by invitation only and are intended to provide expert insight on the state of family medicine and primary health care training in selected African countries.

Word limit	800 words
References	10 or less

Book Reviews

Book reviews are brief articles providing insights or opinions on new books within the research field of the journal. Please contact the editor if you would like to suggest a book for review.

Word limit	1000 words

Scientific Letters

A discussion on a particular topic, whereby the authors raise their opinion on a particular aspect of family medicine and primary health care studies or their reaction to a previously published article in the *African Journal of Primary Health Care & Family Medicine*. This section encourages debate amongst authors and readers on topical issues of national and global importance to the field of family medicine and primary health care studies. Letters will be published at the editors' discretion. In the case of critical letters, the original author will be given an opportunity to provide a short rebuttal which will be published along with the critical letter.

Word limit	2500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words
References	20 or less
Tables/Figures	no more than 1 Tables/Figure

The publication of conference reports are arranged with the Editor-in-Chief.

Word limit	1500 words
References	6 or less
Tables/Figures	no more than 1 Table/Figure

Opinion Papers

Short opinion pieces or personal perspectives (not research papers) personal viewpoint on family medicine and primary health care research that provides a contextual and holistic view of family medicine as practiced across the continent. With rare exceptions, these essays are meant to express a personal viewpoint and should have no more than two authors.

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Structured abstract	250 words
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Tables/Figures	no more than 2 Tables/Figure
Ethical statement	should be included in the manuscript, if applicable

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Word limit	3500-7000 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate
Language	only manuscripts presented in English or French will be considered

Obituaries

Is a news article that reports the recent passing of a person, typically along with an account of the person's work achievement and life.

Word limit	400 words
Photo	a photograph of the deceased

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These must be critical reviews of the literature on topics that have social, economic or scientific values, and must be within the focus and scope of the journal.

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Structured abstract	250 words to cover a Background, Aim, Method, Results and Conclusion
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Language	only manuscripts presented in English or French will be considered

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They may be subjected to the peer review process and their eventual placement is at the discretion of the editorial team. Kindly include include a correspondence address.

Word limit	400 words (excluding the references)
Abstract	n/a
References	10 or less
Tables/Figures	no more than 1 Tables/Figure

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A detailed account of a specific patient as a case study. The patient study should highlight a critical issue that is relevant to the field of family medicine and primary care.

Word limit	1500 words (excluding the unstructured abstract and references)
Unstructured abstract	75 words to cover a Background, Aim, Method, Results and Conclusion
References	15 or less
Tables/Figures	no more than 6 Tables/Figure
Ethical statement	should be included in the manuscript
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- Authors' contributions: Briefly summarise the nature of the contribution made by each of the authors listed.
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- Summary: Lastly, a list containing the number of words, pages, tables, figures and/or other supplementary material should accompany the submission.

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Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

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