EVALUATING ADVERSE DRUG REACTIONS ASSOCIATED WITH ANTIBIOTIC USE IN A PUBLIC SECTOR HOSPITAL

BY

NOKUTHEMBA SIBUSISO MOYO (208525324)

Submitted as the dissertation component in partial fulfilment for the degree of Master of Health Sciences in the School of Health Sciences, University of KwaZulu-Natal.

Date submitted: December 2016

PREFACE

This dissertation is presented in a manuscript format. The findings of the study are presented in chapter 2, in manuscript format as required by the regulations of the University of KwaZulu-Natal. The manuscript will be submitted for publication in the *South African Medical Journal (SAMJ).* The reference list is cited according to the instructions for authors as required by the SAMJ. A complete reference list is included at the end of every chapter and according to the reference style of the University of KwaZulu-Natal.

The dissertation consists of three chapters as follows:

- Chapter 1: provides an introduction to the study as well as the aims, objectives, literature review and a brief overview of the methodology.
- Chapter 2: consists of the results, discussion and conclusion written in a manuscript format.
- Chapter 3: provides the general conclusions, recommendations, limitations and strengths of the study.

ABSTRACT

Background and Aim

Antibiotics are one of the most troublesome classes of drugs contributing to adverse drug reactions. These adverse drug reactions are generally under reported. This study aimed to evaluate the adverse drug reactions associated with antibiotic use in a public sector hospital.

Methods

A prospective, quantitative study was carried out using adverse drug reaction reports collected from a public sector hospital in South Africa, for the period 01 July 2016 – 30 September 2016. All the adverse drug reaction reports attributed to use of antibiotics were included in the study. The patient's age, gender, weight, antibiotic prescribed, dose of antibiotic, route of administration of the antibiotic, adverse drug reaction experienced and action taken regarding the adverse drug reaction was extracted from the adverse drug reaction report. A descriptive and inferential analysis was carried out using SPSS (version 24) to determine the strength of the relationships (Pearson Chi Square test) between different variables.

Results

A total of 10 adverse drug reaction reports were collected during the 3 month period from which 8 were related to antibiotic use (80%). Adverse drug reactions associated with antibiotic use were experienced mostly by female patients (n=6, 75%). Adverse drug reactions were reported for Amphoteracin B (n=3), Amoxicillin (n=1), Cefazolin (n=1), Lopinavir/Ritonavir combination (n=1), Metronidazole (n=1) and Tenofoir/Emtricitrabine/Efavirenz combination (n=1). Of the 8 adverse drug reactions, 7 required intervention to prevent permanent damage/disability. There were 2 serious adverse drug reactions; 1 required hospitalization and the other prolonged hospital stay; the remaining adverse drug reactions were classified as non-serious.

Discussion and Conclusion

Antibiotic related adverse drug reactions constituted 80% of all adverse drug reactions reported in a single hospital. The impact of adverse drug reactions associated with antibiotic use in the public hospital ranged from treatment to manage the adverse drug reaction to hospitalization and the prolongation of hospital stay. This study provides useful information on the current status of adverse drug reactions related to antibiotic use in the public sector in South Africa, and indicates the need for adverse drug reaction reporting in hospitals to ensure safety of medicines and better treatment outcomes.

KEYWORDS

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Adverse drug reaction means a response to a medicine in humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from overdose, misuse or abuse of a medicine.

An **adverse drug reaction report** is a detailed record of all relevant data associated with the use of a medicine in a subject or patient.

Healthcare professionals are medical practitioners, pathologists, dentists, pharmacists, nurses, and other healthcare professionals, including allied healthcare professionals.

Antibiotics are (for the purpose of this study) antibacterials, antivirals, antifungals, antituberculars, antimalarials and anthelmintics.

DECLARATION 1 - PLAGIARISM

I, Nokuthemba Sibusiso Moyo, declare that:

1. The research reported in this thesis, except where otherwise indicated; is my original work.
2. The work described in this thesis has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by me or any other party.
3. This thesis 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 their exact words have been used, then their writing has been placed inside quotation marks, and referenced.
4. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the thesis and in the reference sections.

Signed _____ Date_____

This is to certify that the contents of this thesis are the original work of Ms Nokuthemba Sibusiso Moyo and as the candidate's supervisor; I have approved this thesis for submission.

1. Signed: _____ Name: **Dr. Frasia Oosthuizen** Date: _____

DECLARATION 2 – ETHICS APPROVAL

Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE255/16) - (Annexure 1). Permission was obtained from the Mpumalanga Provincial Department of Health to use the adverse drug reaction reports from Bethal hospital (Annexure 2).

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. My contribution to the project was as follows:

Nokuthemba Sibusiso Moyo: Author – contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of the dissertation.

2. The contributions of others to the project were as follows:

Dr Frasia Oosthuizen: Supervisor – supervision of the concept of the study and guidance with writing of the dissertation and manuscript.

DEDICATION

When you want to succeed as bad as you want to breathe, then you will be successful. I dedicate this thesis and give special thanks to my mother; Nokuthula Moyo, for her unconditional love and support throughout my studies.

ACKNOWLEDGEMENTS

In full appreciation I would like to acknowledge my research supervisor, *Dr Frasia Oosthuizen*, for her assistance, guidance, insights and commitment before and throughout my thesis development.

I sincerely thank the Mpumalanga Provincial Department of Health for allowing me access to the adverse drug reaction reports collected from Bethal hospital, upon which my study was based.

I am grateful to *Mrs Nokuthula Moyo* for inspiring me and for being my pillar of strength, without her encouragement this dissertation would not have been possible.

The grace of the Lord God Almighty enabled me to successfully complete my research, for this reason I can do all things through Christ who strengthens me.

LIST OF ACRONYMS AND ABREVIATIONS

ADR	Adverse Drug Reaction
HCP	Health Care Professional
DoH	Department of Health (South Africa)
PV	Pharmacovigilance
SA	South Africa
SAMJ	South African Medical Journal
SD	Standard deviation
UKZN	University of KwaZulu-Natal
WHO	World Health Organisation

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 1
INTRODUCTION

An adverse drug reaction is a response to a medicine in humans or animals, which is noxious and unintended, and which occurs at any dosage. [1] It can also result from an overdose, misuse or abuse of a medicine. It is, by its very nature, undesirable, untoward, or detrimental to the healthcare process or to the patient. Adverse drug reactions may be mild, moderate or severe. A serious adverse drug reaction at any dose may: 1) result in death, 2) be life threatening, 3) require patient hospitalization, 4) prolong existing hospitalization, or 5) cause a congenital anomaly/birth defect. A reportable adverse drug reaction requires the following minimum information: An identifiable source (reporter) of the information, an identifiable patient, suspected product(s) and suspected reaction(s).

According to the World Health Organization policy on ensuring the safe use of medicines (2004), "*Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse or any other drug related problems"*. Pharmacovigilance relies on: 1) collecting information from reliable scientific resources such as healthcare professionals, consumers and journals; 2) classifying and analyzing the information; and 3) circulating its contents as well as any action taken on a specific drug to all healthcare sectors. The aims of pharmacovigilance are to improve the safety of medicines so as to improve patient care and public health as well as assess the risk of the use of medicines.

Challenges of adverse drug reaction reporting include: under-detection (the inability of healthcare professionals in identifying adverse drug reactions) and under-reporting (healthcare professionals presume that adverse drug reaction reporting may indicate incompetence). Many factors are associated with under-reporting of adverse drug reactions among health care professionals. These factors have been broadly classified in 2009 by Oshikoya et al,[2] as personal and professional characteristics of health care professionals, and their knowledge and attitudes to reporting. These factors include:

- attitudes relating to professional activities (*financial incentives*: rewards for reporting; *legal aspects*: fear of litigation or enquiry into prescribing costs; and ambition to compile or publish a personal case series)
- problems associated with adverse drug reaction related knowledge and attitudes (*complacency*: the belief that very serious adverse drug reactions are well documented by the time a drug is marketed; *diffidence*: the belief that reporting an adverse drug reaction would only be done if there was certainty that it was related to the use of a particular drug; *indifference*: the belief that the single case an individual doctor might observe could not

contribute to medical knowledge; and *ignorance*: the believe that it is only necessary to report serious or unexpected adverse drug reactions)

- excuses made by professionals (*lethargy*: the procrastination and disinterestedness in reporting or lack of time to find a report card and other excuses).

With increased access to newly introduced essential drugs, there is a greater need to monitor and promote their safety and effectiveness. Benefits of adverse drug reaction reporting include: improved quality of care, ensuring patient safety, reduced drug-related problems, better treatment outcomes and changes in drug labelling or removal of medicines from the market.[3]

1.1 Problem and significance of work

The most troublesome classes of drugs contributing to adverse drug reactions are antibiotics; these are responsible for the recorded adverse effects in approximately 16% of cases[4], therefore pharmacovigilance of antibiotics is essential to maintain the safety of antibiotics. Granowitz and Brown[5] state that although adverse events seem to occur in a small proportion of antibiotic courses, the frequency of antibiotic use makes them account for 23% of all adverse events recorded. Antibiotic related adverse drug reactions are generally under reported, this may be due to the lack of training of healthcare workers regarding adverse drug reaction reporting or the lack of public awareness on the need to report suspected adverse drug reactions.

Adverse drug reactions related to antibiotics may result in hospitalization, extended hospital stay or death. They may even occur in hospital due to improper prescribing or due to risk factors like age and multiple drug use. Shamma et al[4] identified an increase in healthcare cost associated with antibiotic adverse drug reactions, due to increased length of hospital stay and the need of interventions including stopping the antibiotic and treating the adverse reaction; concluding that periodic reporting of adverse drug reactions should be done in order to increase drug safety. Hospital-based adverse drug reaction monitoring and reporting programs therefore aim to identify and quantify the risks associated with the use of drugs provided in a hospital setting. This information may be useful in identifying and minimizing preventable adverse drug reactions and may enhance the ability of prescribers to manage adverse drug reactions more effectively.[6]

This study will describe adverse drug reactions related to antibiotic use in a public sector hospital. This information will be useful in providing the current status of the problem in public hospitals, and also identify if there is a need to address this. The results of this study will also hopefully encourage health care professionals to report adverse drug reactions and contribute to the development of strategies for pharmacovigilance at public sector hospitals, which will improve the quality of adverse

drug reaction monitoring and reporting to ensure safer antibiotic use in hospitals.

1.2 Literature review

1.2.1 Adverse drug reactions and antibiotic use

In many countries adverse drug reactions rank among the top 10 leading causes of mortality.[4] In Europe, adverse drug reactions cause a considerable amount of morbidity and mortality. It has been estimated that approximately 5 % of all hospital admissions are caused by adverse drug reactions, that 5 % of hospitalized patients will experience an adverse drug reaction during their hospital stay, and that approximately 197,000 deaths per year are due to adverse drug reactions.[7] In a South African survey, adverse drug reactions were the cause of admission for 6.3% of adults admitted to medical wards, and an additional 6.3% of inpatients developed adverse drug reactions during their hospital stay. Recently, adverse drug reactions were implicated in 16% of deaths in the medical wards of four South African hospitals.[8]

Antibiotics are among the most commonly prescribed drugs in hospitals and they account for 20% to 50% of drug costs. Several studies showed antibiotics as one of the drug groups causing more adverse drug reactions[9] than other drugs. An extensive drug monitoring study was conducted amongst adult inpatients taking antibiotics in the city of Maringá, Southern Brazil, from September 2002 to February 2003. The study found that an inadequate knowledge on antibiotics or lack of information about the patient at the time of prescription were the major factors involved in the occurrence of adverse events.[9] Evaluating the dose, route and duration of treatment when prescribing antibiotics is significant because any of those factors can increase the occurrence of adverse drug reactions.

In a prospective study Lobo et al[6] found antibiotics (vancomycin and ceftriaxone) to be among the most common drugs causing adverse drug reactions. These antibiotics required intervention and increased the hospital stay. Several studies conducted over the past years suggest a high direct relationship between antibiotics and specific adverse effects experienced. Viswanathan et al[10] suggested that there is a potential relationship between linezolid use and hypoglycaemia, while Richard Frothingham[11] identified glucose homeostasis abnormality (GHA) as an adverse drug reaction of gatifloxacin. Lawrence[12] delineated the quantity and outcomes of patients who developed serotonin toxicity while undergoing concurrent therapy with linezolid and medications that increase CNS serotonin concentrations.

Antibiotics are one of the most commonly prescribed drugs in hospitals. The implementation of adverse event monitoring and notification programs in hospital settings is an important

action for the prevention of adverse drug reactions associated with antibiotic use.[9]

1.2.2 Importance of adverse drug reaction reporting in hospitals

Adverse drug reactions have a major impact on public health by imposing a considerable economic burden on the society and the already stretched healthcare systems,[2] therefore post marketing surveillance of drugs is very important in analysing and managing the risks associated with drugs once they are available for use by the general population. According to Tumwikirize et al[13] when studying adverse drug reactions' contribution to patient morbidity and hospitalization in Africa, they found that 4.5–8.4% of all hospital admissions were related to adverse drug reactions, 1.5–6.3% of patients were admitted as a direct result of adverse drug reactions; and 6.3–49.5% of all hospitalized patients developed adverse drug reactions.

Adverse drug reactions are recognized as a common cause of hospital admissions, and they constitute a significant economic burden for hospitals. The proportion of patients admitted with adverse drug reactions ranges from approximately 2.0 to 21.4%, whereas between 1.7 and 25.1% of inpatients are reported to have developed an adverse drug reaction during their hospital stay.[6] Adverse drug reaction reporting is essential in a hospital setting so as to ensure the safety of drugs administered to patients, improving the quality of care, minimizing the length of hospital stay, health care costs and the interventions required.

Reports of adverse drug reactions have become an important component of monitoring and evaluation activities performed in hospitals to ensure drug safety.[6] Hospital-based adverse drug reaction monitoring and reporting programs aim to identify and quantify the risks associated with the use of drugs provided in a hospital setting.[6] Thus periodic reporting of adverse drug reactions should therefore be done to increase drug safety.[4]

Two different methods of collecting adverse drug reaction reports are available. One is traditional adverse drug reaction reporting, which is called "spontaneous reporting." The other is "active surveillance," using a phone-structured interview, ward rounds and chart review, or computer monitoring. Active surveillance, as opposed to spontaneous pharmacovigilance systems, can be defined as the periodic collection of case reports from healthcare data systems. Active surveillance systems, such as ward rounds associated with chart review increase the rate of adverse drug reaction detection and detect more serious adverse drug reactions in a hospital setting.[14]

Spontaneous pharmacovigilance systems are not as effective as active surveillance due to under-reporting and insufficient clinical information; thus, active surveillance programs should be implemented in the hospital setting to ensure patient safety and improve the quality of care. The

implementation of adverse event monitoring and notification programs in hospital settings is an important action for the prevention of these adverse drug reactions. These programs promote active surveillance and encourage their documentation and notification.[9] A comprehensive systems perspective addresses the need for both active and passive approaches to identify medicines-related problems, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of pharmacovigilance activities at all levels of the health system.[3]

1.3 Aim and Objectives

The aim of this study was to evaluate adverse drug reactions associated with antibiotic use in a public sector hospital in South Africa.

Specific objectives were to determine the following:

1.3.1 The number of adverse drug reactions associated with antibiotic use over a 3 month period.

1.3.2 Identification of the antibiotic associated with the highest number of adverse drug reactions.

1.3.3 Clinical profile of antibiotics associated with adverse drug reactions including indication and route of administration.

1.3.4 Classification of adverse drug reactions according to severity.

1.3.5 Classification of adverse drug reactions according to action taken.

1.4 Theoretical framework

A prospective study was performed on adverse drug reactions experienced with antibiotic use in a public sector hospital over a three month period. At the onset of the study clinical meetings with hospital healthcare professionals were held to raise awareness of adverse drug reaction monitoring. This has not been done previously in this hospital. The importance of adverse drug reaction monitoring was highlighted and attendees consisting of doctors and nurses were encouraged to report all suspected adverse drug reactions to a pharmacist in the hospital using an adverse drug reaction reporting form.

Admissions due to adverse drug reactions related to antibiotic use, as well as those occurring during the hospital stay were included in the study. For patients where an adverse drug reaction was suspected, monitoring was done by assessing the progress of the patient daily throughout their hospital stay after action was taken to resolve the adverse drug reaction.

The suspected adverse drug reactions were carefully analysed and documented. All relevant data was recorded e.g. demographic information, indication for antibiotic usage, and routes of administration. Therapy given to treat the antibiotic adverse drug reactions was recorded and response noted.

The severity of the adverse drug reaction was classified as serious or non-serious. Serious adverse drug reactions – (when the patient outcome was death, life threatening, required hospitalization, resulted in disability or a birth defect), and non-serious – (when the patient outcome was not death, not life threatening, did not require hospitalization, did not result in disability or cause a birth defect) were stated.

1.5 Research methodology

1.5.1 Study design

A prospective quantitative study of adverse drug reaction reports associated with antibiotics collected between 01 July 2016 and 30 September 2016.

1.5.2 Setting

The study took place in a 150 bed public sector hospital, Mpumalanga, South Africa.

1.5.3 Subjects/Participants

In-patients (hospital patients).

1.5.4 Sampling

All adverse drug reaction reports were collected over the three month study period.

1.5.5 Data collection/Methods

The total number of admissions from 01 July 2016 to 30 September 2016 due to adverse drug reactions was recorded. The number of admissions due to adverse drug reactions related to antibiotics were calculated and compared to the total number of admissions due to adverse drug reactions. Patient demographics including; age, sex and weight were recorded.

Adverse drug reactions associated with antibiotics were categorized as serious (when the patient outcome was death, life threatening, required hospitalization, prolonged hospitalization, disability or birth defect) and non-serious (when the patient outcome was not death, not life threatening, did not require hospitalization, did not prolong hospitalization, did not result in disability or a birth defect). Action taken to manage the adverse drug reaction was recorded.

1.5.6 Data analysis

Variable	Variable type	Descriptive measures	Analytical method/Statistical test
Age	Continuous	Mean, median, mode, SD	ANOVA
Gender	Categorical	Mean, median, mode SD	ANOVA
Seriousness	Ordinal	Proportion	Chi square
Action taken	Ordinal	Proportion	Chi square

SPSS (computer software) was used for the statistical tests.

1.5.7 Ethical approval

Full ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE255/16) – (ANNEXURE 1), and permission to use the hospital adverse drug reaction reports was obtained from the Mpumalanga Department of Health (ANNEXURE 2).

1.6 Chapter summary

This chapter provided a background and rationale to the study. It also identifies the aim and objectives of the study and a brief overview of the methodology used in the study.

REFERENCES

1. World Health Organization. Pharmacovigilance: Ensuring the Safe Use of Medicines – WHO Policy Perspectives on Medicines. Geneva: WHO, 2004. http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf (accessed on 4 July 2016)

2. Oshikoya KA, Awobusuyi JO. Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria. BMC Clinical Pharmacology. 2009;9:14. doi:10.1186/1472-6904-9-14.

3. Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

4. Shamna M, Dilip C, Ajmal M. A prospective study on Adverse Drug Reactions of antibiotics in a tertiary care hospital. Saudi Pharmaceutical Journal : SPJ. 2014;22(4):303-308. doi:10.1016/j.jsps.2013.06.004.

5. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. Critical Care Clinics. 2008;24:421–442. doi: 10.1016/j.ccc.2007.12.011.

6. Lobo MGA de A, Pinheiro SMB, Castro JGD, Momenté VG, Pranchevicius M-CS. Adverse drug reaction monitoring: support for pharmacovigilance at a tertiary care hospital in Northern Brazil. BMC Pharmacology & Toxicology. 2013;14:5. doi:10.1186/2050-6511-14-5.

7. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Safety. 2015;38(5):437-453. doi:10.1007/s40264-015-0281-0.

8. Mouton JP, Mehta U, Parrish AG. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. British Journal of Clinical Pharmacology. 2015;80(4):818-826. doi:10.1111/bcp.12567.

9. Louro E, Lieber R, Silvana N, Ribeiro, E. Adverse events to antibiotics in inpatients of a

university hospital. Revista de Saúde Pública. 2007, vol.41, n.6, pp.1042-1048.

10. Viswanathan P, Iarikov D, Wassel R, Davidson A, Nambiar S. Hypoglycemia in patients treated with linezolid. Clinical Infectious Diseases. 2014;59(8):e93–e95.

11. Frothingham R. Glucose homeostasis abnormalities associated with use of gatifloxacin. Clinical Infectious Diseases. 2005;41(9):1269–1276.

12. Lawrence KR, Adra M, Gillman PK. Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. Clinical Infectious Diseases. 2006;42(11):1578–1583.

13. Tumwikirize W, Ogwal-Okeng J, Vernby A, Anokbonggo W, Gustafsson L, Lundborg S. Adverse drug reactions in patients admitted on Internal Medicine wards in a district and Regional Hospital in Uganda. African Health Sciences. 2011;11(1):72-78.

14. Yun IS, Koo MJ, Park EH. A Comparison of Active Surveillance Programs Including a Spontaneous Reporting Model for Phamacovigilance of Adverse Drug Events in a Hospital. The Korean Journal of Internal Medicine. 2012;27(4):443-450. doi:10.3904/kjim.2012.27.4.443.

CHAPTER 2

MANUSCRIPT FOR SUBMISSION AND PUBLICATION

2.1 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 "Evaluating adverse drug reactions associated with antibiotic use in a public sector hospital". This manuscript will be submitted to the *"South African Medical journal"* (SAMJ) for publication.

The journal instructions to the author can be viewed in *ANNEXURE 3* or with the following link:
http://www.samj.org.za/index.php/samj/about/submissions

2.2 Manuscript

Evaluating adverse drug reactions associated with antibiotic use in a public sector hospital

Nokuthemba Sibusiso Moyo, Frasia Oosthuizen*
School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Private Bag X54001, Durban 4000, South Africa.

*Corresponding author email: oosthuizenf@ukzn.ac.za
Contact number: 031-2607242 Fax: 031-2607907

ABSTRACT

Background and Aim
Antibiotics are one of the most troublesome classes of drugs contributing to adverse drug reactions. These adverse drug reactions are generally under reported. This study aimed to evaluate the adverse drug reactions associated with antibiotic use in a public sector hospital.

Methods
A prospective, quantitative study was carried out using adverse drug reaction reports collected from a public sector hospital in South Africa, for the period 01 July 2016 – 30 September 2016. All the adverse drug reaction reports attributed to the use of antibiotics were included in the study. The patient's age, gender, weight, antibiotic prescribed, dose of antibiotic, route of administration of the antibiotic, adverse drug reaction experienced and action taken regarding the adverse drug reaction was extracted from the adverse drug reaction report. A descriptive and inferential analysis was carried out using SPSS (version 24) to determine the strength of the relationships (Pearson Chi Square test) between different variables.

Results
A total of 10 adverse drug reaction reports were collected during the 3 month period from which 8 were related to antibiotic use (80%). Adverse drug reactions associated with antibiotic use were experienced mostly by female patients (n=6, 75%). Adverse drug reactions were reported for Amphoteracin B (n=3), Amoxicillin (n=1), Cefazolin (n=1), Lopinavir/Ritonavir combination (n=1), Metronidazole (n=1) and Tenofoir/Emtricitrabine/Efavirenz combination (n=1). Of the 8 adverse drug reactions, 7 required intervention to prevent permanent damage/disability. There were 2 serious adverse drug reactions; 1 required hospitalization and the other prolonged hospital stay; the remaining adverse drug reactions were classified as non-serious.

Discussion and Conclusion
Antibiotic related adverse drug reactions constituted 80% of all adverse drug reactions reported in a single hospital. The impact of adverse drug reactions associated with antibiotic use in the public hospital ranged from treatment to manage the adverse drug reaction to hospitalization and the prolongation of hospital stay. This study provides useful information

on the current status of adverse drug reactions related to antibiotic use in the public sector in South Africa, and indicates the need for adverse drug reaction reporting in hospitals to ensure safety of medicines and better treatment outcomes.

Background and Introduction

An adverse drug reaction is a response to a medicine in humans or animals, which is noxious and unintended, and which occurs at any dosage.[1] It can also result from an overdose, misuse or abuse of a medicine. It is, by its very nature, undesirable, untoward, or detrimental to the healthcare process or to the patient. Adverse drug reactions may be mild, moderate or severe. A serious adverse drug reaction at any dose may: 1) result in death, 2) be life threatening, 3) require patient hospitalization, 4) prolong existing hospitalization, or 5) cause a congenital anomaly/birth defect. A reportable ADR requires the following minimum information: An identifiable source (reporter) of the information, an identifiable patient, suspected product(s) and suspected reaction(s).

According to the World Health Organization policy on ensuring the safe use of medicines (2004), *"Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse or any other drug related problems"*. Pharmacovigilance relies on: collecting information from reliable scientific resources such as healthcare professionals, consumers and journals; classifying and analyzing the information and circulating its contents as well as any action taken on specific drug to all healthcare sectors. The aims of pharmacovigilance are to improve the safety of medicines so as to improve patient care and public health as well as assess the risk of the use of medicines.

Challenges of adverse drug reaction reporting include: under-detection (the inability of healthcare professionals in identifying adverse drug reactions) and under-reporting (healthcare professionals presume that adverse drug reaction reporting may indicate incompetence). With increased access to newly introduced essential drugs, there is a greater need to monitor and promote their safety and effectiveness. Benefits of adverse drug reaction reporting include: improved quality of care, ensuring patient safety, reduced drug-related problems, better treatment outcomes and changes in drug labelling or removal of medicines from the market.[2]

The most troublesome classes of drugs contributing to adverse drug reactions are antibiotics; these are responsible for the recorded adverse effects in approximately 16% of cases.[3] Pharmacovigilance of antibiotics is essential to maintain the safety of antibiotics. Granowitz and Brown,[4] state that although adverse events seem to occur in a small proportion of antibiotic courses, the frequency of antibiotic use makes them account for 23% of all adverse events recorded. Antibiotic related adverse drug reactions are generally under reported, this may be due to the lack of training of healthcare workers regarding adverse drug reaction reporting or the lack of public awareness on the need to report suspected adverse drug reactions.

Adverse drug reactions related to antibiotics may result in hospitalization, extended hospital stay or death. They may even occur in hospital due to improper prescribing or due to risk factors like age and multiple drug use. Shamma et al[3] identified an increase in healthcare cost associated with antibiotic adverse drug reactions, due to increased length of hospital stay and the need of interventions including stopping the antibiotic and treating the adverse reaction; concluding that periodic reporting of adverse drug reactions should be done in order to increase drug safety. Hospital-based adverse drug reaction monitoring and reporting programs therefore aim to identify and quantify the risks associated with the use of drugs provided in a hospital setting. This information may be useful in identifying and minimizing

preventable adverse drug reactions and may enhance the ability of prescribers to manage adverse drug reactions more effectively.[5]

This study will describe adverse drug reactions related to antibiotic use in a public sector hospital. This information will be useful in providing the current status of the problem in public hospitals, and also identify if there is a need to address this. The results of this study will also hopefully encourage health care professionals to report adverse drug reactions and contribute to the development of strategies for pharmacovigilance in public sector hospitals, which will improve the quality of adverse drug reaction monitoring and reporting to ensure safer antibiotic use in hospitals.

Methods

Study sample

The study focused on antibiotic related adverse drug reactions reported in a 150 bed public sector hospital in Mpumalanga, South Africa over the stipulated time frame (01 July 2016 – 30September 2016). A total of 10 adverse drug reaction reports were received, of which 8 were analyzed according to the inclusion criteria of the study.

The inclusion criteria encompassed adverse drug reaction reports associated with the use of antibiotics (for the purpose of this study - antibacterials, antivirals, antifungals, antitubercular, antimalarial and anthelmintics) that were submitted during 01 July 2016 – 30 September 2016. The exclusion criteria includes adverse drug reaction reports that; 1) were incomplete, 2) adverse drug reactions reported for medicines other than antibiotics (e.g. anti-hypertensive medicines) and 3) adverse drug reaction reports received out of the stipulated time frame.

Only 8 adverse drug reaction reports met the criteria and were included for analysis. All of the results are based on information on the adverse drug reaction reporting forms completed by the health care professionals.

Full ethical approval for the study was obtained from the University of KwaZulu-Natal, and permission to use the adverse drug reaction reports was obtained from the Mpumalanga Provincial Department of Health.

Sampling, data collection and analysis

The data in the form of adverse drug reaction reports was captured in Microsoft Office Excel. Data included patient demographics (age, gender, weight) and clinical data (antibiotic(s) that were involved, type of adverse drug reaction reported, intervention and patient outcome). Data was coded using numbers analysed using SPSS (version 24).

Descriptive and inferential analyses were conducted. Descriptive analysis included information on frequencies, percentages, measures of central tendency (e.g. mean, median and mode), and measures of variability (e.g. range, standard deviation and variance). Inferential analysis was carried out to determine the strength of the relationships (Pearson Chi Square test) between different variables. A difference between variables with a p-value of less than 0.05 was considered to be statistically significant. Close attention was paid to the most prevalent types of adverse drug reactions, antibiotic(s) involved, and patient demographics in order to identify if some populations are more at risk of developing adverse drug reactions.

Findings

Adverse drug reactions

A total of 10 adverse drug reaction reports were received for the period 01 July – 30 September 2016, 8 of these reports were linked to the use of antibiotics.

Antibiotics associated with adverse drug reactions were identified as amphoteracin B (n=3), amoxicillin (n=1), metronidazole (n=1), cefazolin (n=1), lopinavir/ritonavir combination (n=1) and the tenofovir/emtricitrabine/efavirenz combination (n=1).

Overview of patient demographics

The majority of adverse drug reaction reports submitted were adverse drug reactions experienced by female patients n=6 (75%) as compared to male patients n=2 (25%). The mean weight of both males and females who experienced adverse drug reactions was 48.2± 27.4kg and the mean age was 33.8 ± 26.7 years old.

Adverse drug reaction reports were received as follows according to age groups: 0-14 n=3 (37.5%); adults n=3 (37.5%), and ≥60 (geriatric) n=2 (25%).

Analysis of Antibiotics related to patient demographics

ADRs were reported for the following antibiotics: amphotericin B (n=3), metronidazole (n=1), cefazolin (n=1), amoxacillin (n=1) tenofovir/emtricitrabine/efavirenz combination (n=1) and lopinavir/ritonavir combination (n=1).

Table 1: Adverse drug reactions reported in relation to the patient demographics

Antibiotic	Male	Female	0-14 years old	30-60years old	>60years old
Amphoteracin B	0	3	0	3	0
Amoxicillin	1	0	1	0	0
Cefazolin	0	1	0	0	1
Lopinavir/Ritonavir	0	1	0	0	1
Metronidazole	0	1	1	0	0
Tenofovir/Emtricitrabine/Efavirenz	1	0	1	0	0

Amphoteracin B caused adverse drug reactions in female patients only (n=3) as did metronidazole (n=1), cefazolin (n=1) and lopinavir/ritonavir combination. Amoxicillin caused an adverse drug reaction in a male patient only (n=1) as did tenofovir/emtricitrabine/efavirenz combination.

In the 0-14 year age group amoxicillin (n=1), metronidazole (n=1), and tenofovir/emtricitrabine/efavirenz combination (n=1) were responsible for the adverse drug reactions. In the 30-60 year age group (n=3) of patients developed adverse drug reactions associated with the use of amphoteracin B. Patients who were ≥60 years old experienced adverse drug reactions caused by the use of cefazolin (n=1) and lopinavir/ritonavir combination (n=1).

Clinical profile of antibiotics associated with adverse drug reactions including indication and route of administration

Table 2: Indication and route of administration of antibiotic

Antibiotic	**Indication**	**Route of administration**
Amphoteracin B(n=3)	Cryptococcal meningitis	Intravenous
Amoxicillin	Malnutrition	Oral
Cefazolin	Infection	Intravenous
Lopinavir/Ritonavir	Human Immunodeficiency Vius	Oral
Metronidazole	Urinary tract infection	Intravenous
Tenofovir/Emtricitrabine/Efavirenz	Human Immunodeficiency Vius	Oral

The intravenous route of administration was used for most antibiotics (n=5) where adverse drug reactions were reported. In only 3 cases antibiotics that were administered orally resulted in an adverse reaction.

Analysis of type adverse drug reactions experienced and seriousness

Table 3: Type and seriousness of adverse drug reactions reported

Antibiotic	**Adverse drug reaction**	**Seriousness**
Amphoteracin B	Shivering	Non-serious
Amphoteracin B	Shivering, fever, swollen arm	Serious (prolonged hospital stay)
Amphoteracin B	Lip sores	Non-serious
Amoxicillin	Rash	Non-serious
Cefazolin	Facial oedema	Non-serious
Lopinavir/Ritonavir	Vomiting	Non-serious
Metronidazole	Vomiting	Non-serious
Tenofovir/Emtricitrabine/Efavirenz	Dizziness	Serious (required hospitalization)

The reported adverse drug reactions and their associated antibiotics are described in Table 3. The most commonly reported adverse drug reaction associated with the use of antibiotics was shivering n=2 and vomiting (n=2). The other adverse drug reactions reported included: rash (n=1), dizziness (n=1), facial oedema (n=1) and lip sores (n=1).

Seriousness was measured by the patients' treatment outcome, as described in Table 3. The majority of the patients (n=7: 87.5%) required an intervention to prevent permanent impairment/damage. One did not require an intervention because the adverse drug reaction resolved on its own (Table 4).

Table 4: Seriousness of the reported adverse drug reactions

N=8	
Seriousness of reported ADRs **n=8**	***Frequency n (%)***
Required intervention	7 (87.5)
Symptoms improved without intervention	1 (12.5)
Resulted in disability	0 (0)
Life-threatening	0 (0)
Patient demised	0 (0)

Action taken regarding the adverse drug reactions

Hydrocortisone injection was given to treat the patients who were shivering, had fever and a swollen arm while injecting amphoteracin B and the rash probably caused by amoxicillin. Aciclovir cream was used to treat lip sores probably caused by amphoteracin B. Metronidazole was changed from the oral formulation to injection to avoid vomiting. Lopinavir/ritonavir combination was changed to atazanavir to avoid vomiting. Fluids were given to flush out the tenofovir/emticitabine/efavirenz combination. The adverse drug reaction experienced by the patient on cefazolin resolved on its own and did not require intervention (Table 5).

Table 5: Adverse drug reactions reported in relation to action taken

Antibiotic	**Adverse drug reaction**	**Action taken**
Amphoteracin B	Shivering	Hydrocortisone injection
Amphoteracin B	Shivering, fever, swollen arm	Hydrocortisone injection
Amphoteracin B	Lip sores	Aciclovir cream
Amoxicillin	Rash	Hydrocortisone injection
Cefazolin	Facial oedema	Did not require intervention
Lopinavir/Ritonavir	Vomiting	Changed to Atazanavir
Metronidazole	Vomiting	Changed from oral to injection
Tenofovir/Emtricitrabine/Efavirenz	Dizziness	Fluids

Discussion

A total of 10 adverse drug reaction reports were collected of which 8 were related to antibiotic use. The small number of adverse drug reactions found in this study could be due to the size of the hospital, short time-frame in which the study was conducted, inclusion of inpatients only, or under-reporting.

Antibiotic related adverse drug reactions constituted 80% of all adverse drug reactions identified in this study. This was significantly high and supports previous studies finding antibiotics contributing to most adverse drug reactions. Antibiotics are among the most commonly prescribed drugs in hospitals thereby increasing their rate of adverse drug reactions.

In this study, amphoteracin B was the antibiotic associated with the highest incidence of adverse reactions reported. This can be due to the high plasma protein binding of amphotericin B as well as slow excretion via the kidneys. Amphoteracin B also has a narrow therapeutic index. Fever, shivering and swollen limbs are known adverse drug reactions of amphoteracin B that were also reported in adverse drug reaction reports in this study. Lip sores is an adverse drug reaction not previously recorded with the use of amphoteracin B. As this adverse drug reaction was not identified during clinical trials, it might help to compile the safety profile of amphoteracin B and hopefully be added onto the list of known adverse reactions under the drug labelling of Amphoteracin B.

The other antibiotics for which adverse drug reaction reports were received e.g. amoxicillin, metronidazole, cefazolin, lopinavir/ritonavir combination and Tenofovir/Emtricitrabine/Efavienz combination, are prone to adverse drug reactions and the adverse drug reactions recorded in this study are all well documented.

Females were found to be at a higher risk of developing adverse drug reactions compared to males, which could be attributed to physiological differences in the pharmacokinetics affecting antibiotics.

In this study one patient was admitted as a direct result of an adverse drug reaction associated with antibiotic use; the other cases were hospitalized patients that developed adverse drug reactions related to antibiotics during their stay in hospital. Only one adverse drug reaction, associated with cefazolin, resolved on its own while all other cases required an intervention to prevent permanent disability and/or impairment. This highlights the importance of identifying adverse drug reactions and taking the necessary action to prevent patient morbidity and mortality.

Previously, adverse drug reaction monitoring was rarely done in the study hospital and previous reporting only focused on outpatients receiving anti-retroviral treatment. This study used both active and passive methods of obtaining adverse drug reactions associated with antibiotic use. The importance of adverse drug reaction in a hospital setting was highlighted in this study because a new adverse drug reaction was identified and the occurrence of known adverse drug reactions was recorded. This will help health care professionals to initiate risk management plans that will minimize and prevent future preventable adverse drug reactions.

South Africa uses a spontaneous reporting system in which health care professionals are responsible for reporting suspected adverse drug reactions. A comprehensive

pharmacovigilance system includes both active and passive surveillance methods and ensures efficient surveillance of adverse drug reactions. This study supports the need for adverse drug reaction monitoring and reporting, indicating that it is essential in a hospital setting so as to ensure the safety of drugs administered to patients by improving the quality of care, minimizing the length of hospital stay, health care costs and the interventions required.

Conclusion

This study found significant adverse drug reactions associated with the use of antibiotics. Knowledge of the most prevalent adverse drug reactions, antibiotics involved, and population groups at risk can help decrease the incidence of adverse drug reactions associated with antibiotic use in all levels of health care in South Africa. The results of this study will hopefully encourage health care professionals to report adverse drug reactions, which will improve the quality of adverse drug reaction monitoring and reporting to ensure safer antibiotic use in hospitals. This will also help all health care professionals to reinforce the goals set out by the Department of Health to help strengthen strategies to maximize patient safety, ensure rational use of medicines, and reduce healthcare costs caused by adverse drug reactions at the primary level of healthcare.

REFERENCES

1. World Health Organization. Pharmacovigilance: Ensuring the Safe Use of Medicines – WHO Policy Perspectives on Medicines. Geneva: WHO, 2004. http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf (accessed on 4 July 2016)

2. Strengthening Pharmaceutical Systems (SPS) Program. 2011. Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

3. Shamna M, Dilip C, Ajmal M. A prospective study on Adverse Drug Reactions of antibiotics in a tertiary care hospital. Saudi Pharmaceutical Journal : SPJ. 2014;22(4):303-308. doi:10.1016/j.jsps.2013.06.004.

4. Granowitz EV, Brown RB. Antibiotic adverse reactions and drug interactions. Critical Care Clinics. 2008;24:421–442. doi: 10.1016/j.ccc.2007.12.011

5. Lobo MGA de A, Pinheiro SMB, Castro JGD, Momenté VG, Pranchevicius M-CS. Adverse drug reaction monitoring: support for pharmacovigilance at a tertiary care hospital in Northern Brazil. BMC Pharmacology & Toxicology. 2013;14:5. doi:10.1186/2050-6511-14-5.

CHAPTER 3
CONCLUSIONS

3.1 Introduction

This study was carried out to evaluate the adverse drug reactions, associated with antibiotic use, in a public sector hospital.

3.1.1 Strengths of the study methodology and design

Data sets used in the study were obtained using adverse drug reaction reports therefore making data collection cost-effective.

3.2 Conclusions drawn from the study findings

The aim of this study was to evaluate adverse drug reactions associated with antibiotic use in a public sector hospital with reference to the antibiotics involved, adverse drug reactions in relation to patient demographics, types and seriousness of adverse drug reactions reported, and interventions required. To achieve this, the following specific objectives were outlined:

- The number adverse drug reactions associated with antibiotic use was determined.
- The antibiotic with the highest number of adverse drug reactions was identified.
- Clinical profile of antibiotics including indication and route of administration.
- Adverse drug reactions were classified according to severity.
- Adverse drug reactions were classified according to action taken.

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

- Antibiotic related adverse drug reactions constituted 80% of all adverse drug reactions reported. This was significantly high and suggests that antibiotics contribute to most adverse drug reaction reports. Antibiotics are among the most commonly prescribed drugs in hospitals thereby increasing their rate of adverse drug reactions. This can also be attributed to the mechanism of action of the antibiotics involved.
- The most commonly reported antibiotic associated with adverse drug reactions was Amphoteracin B (n=3; 37.5%). Amphoteracin B is highly bound onto plasma proteins and it is excreted slowly via the kidneys. Amphoteracin B furthermore has a narrow therapeutic index. Fever, shivering and swollen arm are known adverse drug reactions of amphoteracin B. Lip sores is a new adverse drug reaction seen with the use of amphoteracin B in this study.

- Intravenous route (n=5) was the most common route of administration of the antibiotics in this study and could have enhanced adverse drug reactions due to the immediate therapeutic effect.
- The impact of adverse drug reactions associated with antibiotic use in the public hospital were serious in 2 cases, one required hospitalization and the other prolongation of hospital stay. This could have been attributed to the mechanism of action of the antibiotics involved.
- A considerably high rate of patients n=7 (87.5%) required an intervention to prevent permanent disability and/or impairment. Patients that required an intervention (either a change in regimen, a supplementary drug or therapy to treat the adverse drug reaction) Only one adverse drug reaction associated resolved on its own.

3.3 Significance of the study

- The study will encourage health care professionals in the public sector to practice active and spontaneous adverse drug reaction reporting. This information will be useful for identifying and minimizing adverse drug reactions and may enhance the ability of prescribers to manage adverse drug reactions more effectively.

- The study will contribute to the development of strategies for the pharmacovigilance service at the public sector hospital, which will improve the quality of adverse drug reaction monitoring and reporting to ensure safer drug use in the hospital. It will improve the classification and management of serious and non-serious adverse drug reactions in the public sector hospital.

- This study will describe the experiences of adverse drug reactions related to antibiotics in a public sector hospital.

3.4 Limitations of the study

- Sample size: small due to a few adverse drug reactions reported during the study period and the focus only on hospital patients.

- Incomplete or inaccurate reporting: A small proportion of adverse drug reactions being reported and reports containing limited information. Relevant data, such as underlying

medical conditions, concurrent medications, and temporal associations were absent. Information provided in adverse drug reaction reports was highly variable; some reports quite detailed, whereas others provided little data.

- Bias

  - Population bias- the use of adverse drug reaction reports obtained from the public sector hospital only and data collected from hospital patients only.
  - Detection bias- it may have not be easy to classify an adverse drug reaction. A causal relationship between an antibiotic and event could have not been established.
  - Reporting bias- clinicians have different perceptions about specific drugs. Many factors can influence whether or not an event is reported

- Time constraints: Short period (3 months) for the study.

- Underreporting: clinicians fear that adverse drug reaction reporting means that they are incompetent.

- The data obtained and used in this study was restricted to a public-sector hospital

- The use of complementary and/or herbal medicines by these patients was not considered in this study. Only medicines that patients were receiving from the hospital were considered. Therefore, drug interactions amongst herbal/complementary medicines with antibiotics were not considered in terms of possibly causing the adverse drug reaction or influencing its outcome**.**

3.5 Recommendations

- Adverse drug reaction reports from both public-sector and private-sector can provide a broader insight when studying adverse drug reactions associated with antibiotic use. Therefore, further studies should incorporate both sectors.

- Avoiding unnecessary antibiotic use reduces not only the public health threat of antibiotic resistance but also the risk of adverse drug reactions in individual patients, therefore appropriate use of antibiotics should be upheld.

- Further studies on the topic should take into consideration herbal/complementary medicines that patients use to treat concomitant diseases and their possible drug-drug interaction(s) with antibiotics as this could possibly influence the outcome of adverse drug reactions.

3.6 Chapter summary

The final chapter highlighted the conclusions drawn from the findings of the study, described the strengths and limitations of the study, as well as provided recommendations for future research.

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 June 2016

Ms NS Moyo (208525324)
Discipline of Occupational Therapy
School Of Health Sciences
Nokuthemba.moyo@gmail.com

Dear Ms Moyo

Protocol: Evaluating adverse drug reactions associated with antibiotic use in a public sector hospital.
Degree: M-Pharm
***BREC reference* number: BE255/16**

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 06 April 2016.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 22 June 2016 to queries raised on 20 June 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval.**

This approval is valid for one year from **28 June 2016.** 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 meeting taking place on **16 August 2016.**

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

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: oosthuizenf@ukzn.ac.za postgraduate office: nenep1@ukzn.ac.za

health
MPUMALANGA PROVINCE
REPUBLIC OF SOUTH AFRICA

No 3, Government Boulevard, Riverside Park, Ext. 2, Mbombela, 1200, Mpumalanga Province
Private Bag X11285, Mbombela, 1200, Mpumalanga Province
Tel I: +27 (13) 766 3429, Fax: +27 (13) 766 3458

Litiko Letemphilo | Departement van Gesondheid | UmNyango WezeMaphilo

Enquiries: Themba Mulungo (013) 766 3511

12 July 2016

Ms. Nokuthemba Moyo
P.O Box 5050
Krugersdorp West
1742

Dear Ms. Nokuthemba Moyo

APPLICATION FOR RESEARCH & ETHICS APPROVAL: EVALUATING ADVERSE DRUG REACTIONS ASSOCIATED WITH ANTIBIOTICS IN A PUBLIC SECTOR HOSPITAL

The Provincial Health Research and Ethics Committee has approved your research proposal in the latest format that you sent.

PHREC REF: MP_2016RP56_968

Kindly ensure that you provide us with the soft and hard copies of the report once your research project has been completed.

MPUMALANGA PROVINCE
DEPARTMENT OF HEALTH
PLANNING & INFORMATION
2016 -07- 12
DATE
PRIVATE BAG X11285
NELSPRUIT 1200

Kind regards

MR. JERRY SIGUDLA
RESEARCH AND EPIDEMIOLOGY

MPUMALANGA
THE PLACE OF THE RISING SUN

ANNEXURE 3

SAMJ Author Guidelines

Submissions

- » Online Submissions
- » Author Guidelines
- » Copyright Notice
- » Privacy Statement

Online Submissions

Already have a Username/Password for South African Medical Journal? GO TO LOGIN

Need a Username/Password? GO TO REGISTRATION

Registration and login are required to submit items online and to check the status of current submissions.

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Research articles (previously 'Original articles') not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to clinical medicine and related fields. *References should be limited to no more than 15.* Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters will be considered for publication as shorter ***Research articles***.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the *SAMJ* peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Forum articles must be accompanied by a short description (50 words) of the affiliation details/interests of the author(s). Refer to recent forum articles for guidance. Please provide an accompanying abstract not exceeding 150 words.

Book reviews should be about 400 words and must be accompanied by the publication details of the book.

Obituaries should be about 400 words and may be accompanied by a photograph.

Guidelines must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed. A structured abstract not exceeding 250 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2. etc.) and summarised in a Table of Contents. References, appendices, figures and tables must be kept to a minumum.

Guidelines exceeding 8 000 words will only be considered for publication as a supplement to the SAMJ*; the costs of which must be covered by sponsorship or advertising. The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.*

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached individually as '**supplementary files**' upon submission (not solely embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES

References must be kept to a maximum of 15. Authors must verify references from original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given.

Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID). Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal

communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

CHANGES OF ADDRESS

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

CPD POINTS

Authors can earn up to 15 CPD CEUs for published articles. Certificates may be requested after publication of the article.

CHARGES

There is no charge for the publication of manuscripts.

Please refer to the section on '*Guidelines*' regarding the publication of supplements, where a charge may be applicable.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word or RTF document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)

10. Any conflict of interest (or competing interests) is indicated by the author(s).