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

BY

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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: ______________

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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.
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<td>Adverse Drug Reaction</td>
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<tr>
<td>HCP</td>
<td>Health Care Professional</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health (South Africa)</td>
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<td>PV</td>
<td>Pharmacovigilance</td>
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<td>South African Medical Journal</td>
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## CHAPTER 1

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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 belief 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 cases4, therefore pharmacovigilance of antibiotics is essential to maintain the safety of antibiotics. Granowitz and Brown5 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 al4 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. 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. 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.

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 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. 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 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 suggested that there is a potential relationship between linezolid use and hypoglycaemia, while Richard Frothingham identified glucose homeostasis abnormality (GHA) as an adverse drug reaction of gatifloxacin. Lawrence 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 al13 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.
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. 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.

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

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<tr>
<td>Action taken</td>
<td>Ordinal</td>
<td>Proportion</td>
<td>Chi square</td>
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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


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


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:
2.2 Manuscript

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

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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 Amphotericin 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 – 30 September 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 amphotericin B (n=3), amoxicillin (n=1), metronidazole (n=1), cefazolin (n=1), lopinavir/ritonavir combination (n=1) and the tenofovir/emtricitabine/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), amoxicillin (n=1) tenofovir/emtricitabine/efavirenz combination (n=1) and lopinavir/ritonavir combination (n=1).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Male</th>
<th>Female</th>
<th>0-14 years old</th>
<th>30-60 years old</th>
<th>&gt;60 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tenofovir/Emtricitabine/Efavirenz</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Amphotericin 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/emtricitabine/efavirenz combination.

In the 0-14 year age group amoxicillin (n=1), metronidazole (n=1), and tenofovir/emtricitabine/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 amphotericin 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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Indication</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Amphotericin B</em>(n=3)</td>
<td>Cryptococcal meningitis</td>
<td>Intravenous</td>
</tr>
<tr>
<td><em>Amoxicillin</em></td>
<td>Malnutrition</td>
<td>Oral</td>
</tr>
<tr>
<td><em>Cefazolin</em></td>
<td>Infection</td>
<td>Intravenous</td>
</tr>
<tr>
<td><em>Lopinavir/Ritonavir</em></td>
<td>Human Immunodeficiency Virus</td>
<td>Oral</td>
</tr>
<tr>
<td><em>Metronidazole</em></td>
<td>Urinary tract infection</td>
<td>Intravenous</td>
</tr>
<tr>
<td><em>Tenofovir/Emtricitrabine/Efavirenz</em></td>
<td>Human Immunodeficiency Virus</td>
<td>Oral</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adverse drug reaction</th>
<th>Seriousness</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Amphotericin B</em></td>
<td>Shivering</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Amphotericin B</em></td>
<td>Shivering, fever, swollen arm</td>
<td>Serious (prolonged hospital stay)</td>
</tr>
<tr>
<td><em>Amphotericin B</em></td>
<td>Lip sores</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Amoxicillin</em></td>
<td>Rash</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Cefazolin</em></td>
<td>Facial oedema</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Lopinavir/Ritonavir</em></td>
<td>Vomiting</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Metronidazole</em></td>
<td>Vomiting</td>
<td>Non-serious</td>
</tr>
<tr>
<td><em>Tenofovir/Emtricitabine/Efavirenz</em></td>
<td>Dizziness</td>
<td>Serious (required hospitalization)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>N=8</th>
<th>Seriousness of reported ADRs***</th>
<th>Frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=8</td>
<td>Required intervention</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td></td>
<td>Symptoms improved without intervention</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Resulted in disability</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Life-threatening</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Patient demised</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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 amphotericin B and the rash probably caused by amoxicillin. Aciclovir cream was used to treat lip sores probably caused by amphotericin 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/emtricitabine/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

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adverse drug reaction</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>Shivering</td>
<td>Hydrocortisone injection</td>
</tr>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>Shivering, fever, swollen arm</td>
<td>Hydrocortisone injection</td>
</tr>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>Lip sores</td>
<td>Aciclovir cream</td>
</tr>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>Rash</td>
<td>Hydrocortisone injection</td>
</tr>
<tr>
<td><strong>Cefazolin</strong></td>
<td>Facial oedema</td>
<td>Did not require intervention</td>
</tr>
<tr>
<td><strong>Lopinavir/Ritonavir</strong></td>
<td>Vomiting</td>
<td>Changed to Atazanavir</td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>Vomiting</td>
<td>Changed from oral to injection</td>
</tr>
<tr>
<td><strong>Tenofovir/Emtricitabine/Efavirenz</strong></td>
<td>Dizziness</td>
<td>Fluids</td>
</tr>
</tbody>
</table>
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, amphotericin 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. Amphotericin B also has a narrow therapeutic index. Fever, shivering and swollen limbs are known adverse drug reactions of amphotericin 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 amphotericin B. As this adverse drug reaction was not identified during clinical trials, it might help to compile the safety profile of amphotericin B and hopefully be added onto the list of known adverse reactions under the drug labelling of Amphotericin B.

The other antibiotics for which adverse drug reaction reports were received e.g. amoxicillin, metronidazole, lopinavir/ritonavir combination and Tenofovir/Emtricitabine/Efavirenz 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


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 Amphoteracinc B (n=3; 37.5%). Amphoteracinc B is highly bound onto plasma proteins and it is excreted slowly via the kidneys. Amphoteracinc B furthermore has a narrow therapeutic index. Fever, shivering and swollen arm are known adverse drug reactions of amphoteracinc B. Lip sores is a new adverse drug reaction seen with the use of amphoteracinc 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.
Ms NS Moyo (208525374)
Discipline of Occupational Therapy
School Of Health Sciences
Nokuthamba.moyo@gmail.com

Dear Ms Moyo

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.


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 Tsoska-Gwagweni
Chair: Biomedical Research Ethics Committee

cc supervisor: osthutzenf@ukzn.ac.za postgraduate office: nene1@ukzn.ac.za
Dear Ms. Nokuthamba 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.

Kind regards

MR. JERRY SIGUDLA
RESEARCH AND EPIDEMIOLOGY

12 July 2016
ANNEXURE 3

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