PREVALENCE AND DETERMINANTS OF ANTIBIOTIC RELATED ADVERSE DRUG REACTIONS IN KENYA: SPONTANEOUSLY REPORTED CASES AT THE PHARMACY AND POISONS BOARD DATABASE

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DEDICATION

I dedicate this work to Ng'ash and little J.

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ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
AMR	Antimicrobial resistance
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GIT	Gastrointestinal tract
HIV	Human Immunodeficiency Syndrome
ICSR	Individual case safety report
KNH	Kenyatta National Hospital
MDR-TB	Multidrug resistant tuberculosis
PPB	Pharmacy and poisons board
PV	Pharmacovigilance
RHZE	Rifampicin/ Isoniazid/ Pyrazinamide/ Ethambutol
S	Streptomycin
SJS	Steven-Johnson Syndrome
TB	Tuberculosis
TEN	Toxic epidermal necrolysis
URTI	Upper respiratory infection

US	United States of America
UoN	University of Nairobi
WHO	World Health Organization

OPERATIONAL TERMS

Spontaneous reporting	Voluntary reporting of adverse effects of suspected harm from a medicine by health professionals or patients to the national pharmacovigilance center
ICSR	A document for the reporting of a suspected adverse reaction to a medicinal product that has occurred in an individual patient
ADR	An unwanted or undesirable effect of a medication that occurs following the use of a drug under normal clinical use

ABSTRACT

Introduction: Antibiotics are used for treatment and prophylaxis of various infectious conditions and are considered as safe drugs when used rationally. Like all other drugs, they also cause adverse drug reactions in various patient conditions and many studies reveal that the incidence of adverse drug reactions could be higher in case of antibiotics. Adverse drug reactions contribute significantly to morbidity and mortality globally. The impact of adverse reactions include their effect on patient adherence to treatment, treatment outcomes and the development of antimicrobial resistance. Some of the documented reactions due to antibiotics include gastrointestinal reactions, skin reactions and liver injury among others.

In Kenya, the Pharmacy and Poisons Board (PPB) is mandated to carry out pharmacovigilance activities in the country. The national pharmacovigilance system was established in 2004. In 2010, Kenya became a member of the World Health Organization - Program for International Drug Monitoring (PIDM). Individual case safety reports are submitted by healthcare workers to the PPB voluntarily to alert the regulatory body of suspected adverse drug reactions.

Objective: The main aim of this study was to describe the prevalence and characteristics including the type, severity and outcome of adverse drug reactions (ADRs) due to antibiotics from the spontaneous reporting database in Kenya from January 2010 to December 2015.

Methodology: A retrospective cross sectional study was carried out at the Pharmacy and Poisons Board. Spontaneously reported individual case safety reports (ICSRs) submitted between January 2010 and December 2015 to the national database were reviewed. Universal sampling was used. A pre-designed data collection form adopted from the Suspected Adverse Drug Reaction Reporting Form was used to collect data. Information on the patients' biodata, diagnosis, description of the ADR, details of the suspected drug, concomitant medicines used, severity of the reaction, outcome of the reaction and causality assessment was abstracted from the ICSRs. Data was obtained from both manually filed and computerized reports. Data analysis was conducted using Stata version 13.

Results: A total of 550 ICSRs were analyzed. There were more females (60.0%) with ADRs due to antibiotics compared to males (36.6%). The median age of the cases was 34 [IQR 22.0-45.0] years. The most affected organ systems was the integumentary system (60.9%)

with skin rash (39.7%) as the most commonly reported ADR. The antibiotic classes reported to have caused the most ADRs were sulphonamides (34.69%) followed by anti-tuberculosis agents (16.2%). Cotrimoxazole was suspected to cause the majority (56%) of the ADRs. The severity assessment revealed that most of the reported ADRs were moderate (50.7%) and mild (31.9%) with 83.2% of the suspected drug being withdrawn. Complete recovery was reported in 28.5% of the cases while 42.5% were in the process of recovering at the time of reporting the ADR. Age was reported to be associated with the severity of the reported ADRs while HIV status and the severity of the reported ADR were associated with an increased risk of having an undesirable outcome or no recovery. Causality assessment was done which showed that 66.2% of the reactions were probable, and 18.3% were certain to have been caused by the suspected antibiotic.

Conclusion: This study showed the high burden of antibiotic related morbidity and mortality in adults taking antibiotics. Due to the nature of the reported ADRs, majority of the cases required an intervention to manage them. Antibiotics were also suspected to have contributed to fatalities during the six year period (2010-2015). This study found that most of the reported ADRs affected the skin. Majority of the ADRs occurred in HIV positive patients taking cotrimoxazole as a prophylaxis for opportunistic infections. The HIV status of the patients and severity of the ADRs put the patients at risk of having undesirable outcomes, including no recovery. The findings emphasize the importance of monitoring all patients on antibiotics especially HIV positive patients as well as children and the elderly who experienced more severe ADRs.

CHAPTER ONE: INTRODUCTION

1.1. Background

Antibiotics are medicines used for treatment and prophylaxis of different infectious disease conditions. Similar to all other drugs however, they also cause adverse drug reactions (ADRs) in varied patient conditions and many studies have revealed that the occurrence of ADRs is more common with the use of antibiotics compared to other classes of medicines (1). Antibiotic use accounts for about 11% of iatrogenic disease (2). Even though ADRs appear to arise in a small percentage of antibiotic therapy cases, the regularity of antibiotic consumption makes them constitute 23% of all ADRs reported (1).

An adverse drug reaction has been defined by the World Health Organization (WHO) as a response to a drug that is noxious, unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of a physiological function (3). Adverse drug reactions are a global problem of major concern. The negative effects associated with medicines of substandard quality, medication errors and adverse drug reactions contribute notably to morbidity, mortality and reducing patients' quality of life globally. ADRs account for the highest percentage of iatrogenic illnesses, complicating 5-15% of therapeutic drug use (4). Generally, 5-25% of hospital admissions are as a result of ADRs and 6-15% of hospitalized patients present with major adverse drug reactions, resulting in marked lengthening of hospital stay (5). Though most cases of ADRs may go unidentified especially in developing countries, data from developed countries like the United States of America (US) and the European Union (EU) approximate adverse drug events as the 4th to 6th main cause of mortality (6).

Though there is scarce data on antibiotic consumption in Kenya, studies have shown that developing countries contributed 76% of the global rise in antibiotic consumption between 2000 and 2010. The rise in antibiotic use, steered by an advance in economic growth, poses a significant threat to public health by increasing the risk of antibiotic associated ADRs (7). The high burden of HIV/AIDS especially in sub-Saharan Africa has contributed to an increase in antibiotic use for prophylaxis of opportunistic infections as well as for treatment of co-morbidities such as tuberculosis (TB). This implies an increased risk of antibiotic-linked ADR (8).

1.2. Problem statement

Studies have shown that antibiotics account for up to 40% of reported ADRs (9,10) and the reactions can sometimes lead to serious outcomes including hospitalization. However, few reports on ADRs have evaluated only antimicrobial agents.

Antibiotics are widely and at times inappropriately used in all public and private sector settings. Prescription only medicines including antibiotics, are readily available in Kenya and can easily be obtained over the counter without a prescription. A study carried out to determine the pattern of antibiotic sale in retail chemists in Nairobi determined that about 64% of chemists sell antibiotics without prescriptions from prescribers. Potential hazards of self-medication habits include severe ADRs due to antibiotic use (11,12).

Adverse drug reactions due to antibiotics have not been focused on as much as antibiotic resistance (AMR). AMR resulting from increased use of antibiotics is deemed to be a major threat to public health (13). As a result, efforts to encourage prudent use of antibiotics have focused primarily on the long-term public impact of antibiotic resistance. The more immediate hazards of antibiotic use in the community, that is, adverse reactions are generally regarded as sporadic and mild. National campaigns and communication strategies targeted at antibiotic stewardship have not traditionally included information that address these adverse reactions. Factors that contribute to development of antimicrobial resistance include poor patient compliance. This can arise from poor adherence to antibiotic treatment due to ADRs (14).

The management of infectious diseases in Kenya mainly follows set treatment guidelines. However, patients are still susceptible to ADRs.

1.3. Study justification

There are few publications of ADRs due to antibiotics especially in Africa. There is therefore need to study and document this information to determine the burden of antibiotic-related ADRs. This study has endeavored to ascertain the prevalence, types and severity of ADRs due to antibiotics submitted through the pharmacovigilance system in Kenya. The study has further revealed the impact of antibiotics associated ADRs on patients including hospitalization or prolonged hospitalization, development of congenital anomalies,

requirement of interventions to prevent permanent damage and even death, in a vast and diverse population.

The findings of this study will help improve the management of patients on antibiotics as well as improve on patient safety. The findings will also inform any policy changes required on antibiotic use in the country as well as any changes required in the standard treatment guidelines in the use of antibiotics.

1.4. Research Question

What is the prevalence and types of antibiotic related adverse drug reactions reported in Kenya for the period between January 2010 and December 2015?

What is the severity and outcomes of spontaneously reported adverse drug reactions due to antibiotics from the database in Kenya for the period between January 2010 and December 2015?

1.5. Objectives

1.5.1. Main Objective

The main objective of this study was to describe the prevalence and characteristics of spontaneously reported adverse drug reactions which include the type, severity and outcome of antibiotic related ADRs by evaluating the Individual Case Safety Reports at the PPB for the period January 2010 to December 2015.

1.5.2. Specific Objectives

1. To determine prevalence and types of antibiotic related adverse drug reactions in Kenya
2. To describe the severity, outcomes and risk factors associated with antibiotic related adverse drug reactions in Kenya
3. To describe the regulatory actions taken by the Pharmacy Poisons Board following reporting of antibiotic related adverse drug reactions

CHAPTER TWO: LITERATURE REVIEW

2.1. Antibiotics use

Antibiotic usage has led to the significant decrease in morbidity caused by communicable and infectious illnesses in the last 5 decades worldwide. A significant percentage of the total drug budget in many countries is allocated to antibiotics and they are often the largest single group of medicines procured in developing countries (15).

Antibiotics are any of different chemical substances, produced by various microorganisms, especially fungi, or manufactured synthetically and are able to kill or inhibit the growth of microorganisms, notably bacteria (16,17). Antibiotics target microorganisms such as bacteria and parasites. However, they are not effective against viruses. The main classes of natural antibiotics that are obtained from fungi and bacteria include penicillins, cephalosporins, aminoglycosides, tetacyclins, macrolides and anti-tuberculosis drugs. Classes of synthetic antibiotics that are in clinical use are the sulphonamides, quinolones and oxazolidinones (18). The various antibiotic classes may differ with regards to their mechanism of actions and adverse reactions.

Antibiotics are drugs used for chemotherapy of various infectious diseases and are regarded as safe medicines when used appropriately. Similar to other medicines however, antibiotics also exhibit adverse drug reactions in varied user statuses with some studies reporting that the occurrence of ADRs is higher in the case of antibiotics (19). Past occurrence of ADRs can predict risk of future drug use and occurrence of ADRs and may necessitate mitigation or definite treatment of the effects. Management of ADRs includes adjustment of the dosage being used, stopping therapy if possible and definitive treatment of the ADR. Suspected ADRs should be communicated to the relevant authorities. Surveillance techniques can identify reactions and verify associations (20).

2.2. Adverse Drug Reactions due to antibiotics

Antibiotics are presently the most frequently prescribed medicines in health facilities, globally. More than 50% of all hospitalized patients are managed with various types of antibiotics and studies also report that antibiotics use account for 20–50% of medicine costs

in health facilities. The overall medical costs linked to the use of antibiotics are associated not only to antibiotic consumption on its own, but also to ADRs (19).

Adverse reactions can be categorized into two groups; type A (intrinsic/pharmacological reactions) or type B (idiosyncratic reactions). Pharmacological reactions occur more frequently, accounting for about 80% of all ADRs. These reactions result directly from magnification of the known pharmacological activity of the medicine. The reactions are commonly linked to the dosage used and are caused by the pharmacological attributes of the drug. Aspects that make a patient susceptible to these ADRs comprise of dosage of the drug, differences in drug formulation, pharmacokinetic or pharmacodynamic anomalies, drug-drug interactions, drug-food interactions or concomitant illness. Pharmacological adverse reactions develop once drug levels in the body surpass the "therapeutic window" or in case there is a rise in responsiveness to the medicine (even at normal therapeutic levels). They are predictable with most identified prior to marketing of the drug. Pharmacological reactions are associated with high morbidity and low mortality (21,22).

Type B (idiosyncratic) ADRs are not predictable, not frequent, and mostly severe, not linked to the dosage used and do not display a straight forward association between the dosage used and the development of an ADR or its seriousness. The ADRs can be influenced by genetic and environmental factors The mechanism involved in idiosyncratic reactions is largely unknown but is hypothesized to involve receptor irregularities, anomalies of a biological system that is revealed by the medicine, immunological reaction, drug-drug interactions, or can due to more than one aspect (21,22). Idiosyncratic ADRs do not have an association with the pharmacological activity of the drug. They're associated with high mortality and are frequently not discovered until after a drug is marketed.

2.2.1. Adverse drug reactions due to beta lactam antibiotics

Penicillin allergy is uncommon with life threatening anaphylaxis occurring in 1-5 users per 10 000 patients on therapy. Anaphylactic reactions can be fatal and the symptoms include a drop in blood pressure, difficulty in breathing due to bronchoconstriction, seizures and loss of consciousness. Hypersensitivity reactions are the major adverse reactions associated with the use of penicillins. Hypersensitivity presents as nausea, vomiting, diarrhea, pruritus, hives, difficulty in breathing, laryngeal oedema, and eventually, cardiac arrest (23). There are 2 clinical presentations which may occur from an allergy to this group of drugs. These are acute reactions mediated by IgE antibodies and sub-acute reactions mediated by IgG antibodies.

The acute allergic reaction develops instantly and fast in a few minutes to 1-2 hours. The reaction involves abrupt anaphylaxis with a decrease in blood pressure, asthma, rhinitis, angioedema and urticaria. Acute reactions originate from reaction between preformed IgE and penicillin. The IgE antibodies are formed during a past exposure that may not have produced any detectable reactions. The IgE antibodies bind to mast cells and basophils resulting in a release of histamine and other mediators giving rise to a presentation characteristic of a classic anaphylactic reaction. A less marked reaction can develop seven to ten days following initiation of therapy or one to two days following recurrent therapy. In this case, the reaction will be sub-acute and may comprise hives, fever and joint pain or arthritis. This sub-acute reaction arises from a reaction between preformed IgG (from past penicillin use) and penicillin. The IgG antibody binds to penicillin forming an immune complex resulting in the activation of the complement system leading to inflammation. The inflammation causes the development of symptoms referred to previously on the organs where the immune complexes are deposited (23,24).

Cephalosporins are generally associated with fewer ADRs. The frequent reactions involve the GIT such as stomach cramps or unsettled stomach, nausea, vomiting and diarrhea. The reactions are normally not severe and the symptoms resolve after a while. Major but uncommon ADRs which may develop after cephalosporin therapy include black and bloody stools, chest pain, fever, dysuria, anaphylactic shock and severe colitis. Severe colitis is a rare reaction which manifests as serious stomach cramps, acute watery diarrhea (that may contain blood or mucus), fever and general body weakness (25).

2.2.2. Adverse drug reactions due to macrolides

Among the macrolides, erythromycin is associated with a higher incidence of gastrointestinal adverse reactions compared to the other drugs in that class, with 5 - 30% of users experiencing symptoms. The GIT reactions are dose dependent and occur more frequently in children (26). Though short term deafness and allergic reactions to macrolides are not common, they have been shown to occur more frequently following medication with erythromycin as compared to other drugs in this class (27). Of the anti-microbials suspected of interfering with the QT interval (such as some fluoroquinolones, macrolides, azole antifungals, and pentamidine), there are suggestions that macrolides have the highest possibility of causing QT interval prolongation and torsade de pointes. Some possible consequences of macrolide use on the QT interval are; inherent prolongation of the QT

interval, and the ability to inhibit the metabolism of other medicines (such as quinine) which themselves cause prolongation of the QT interval at raised plasma levels. This is due to inhibition of cytochrome P450 enzymes. These two effects are especially linked to erythromycin and clarithromycin (28).

2.2.3. Adverse drug reactions due to quinolones

The most frequent ADRs linked to the quinolone group of antibiotics affect the GIT especially nausea and diarrhea as well as central nervous system (CNS) reactions, particularly headache and dizziness. The ADRs are usually not serious and do not require any adjustment in treatment. Major quinolone-related ADRs affect the cardiovascular system (QT interval prolongation), musculoskeletal system (inflammation of the tendons and tendon rupture), endocrine system (glucose homeostasis dysregulation), renal system (crystalluria, acute renal failure), and the CNS (seizures) (29,30). These adverse reactions can impact on a patient's ability to tolerate these drugs.

2.2.4. Adverse drug reactions due to sulphonamides

Among sulphonamide drugs, cotrimoxazole which is a fixed-dose combination of sulfamethaoxazole and trimethoprim is the most widely used. In 2006, WHO issued guidelines recommending the use of cotrimoxazole in the prophylaxis of opportunistic infections in HIV-exposed children, children living with HIV and adolescents and adults living with HIV (31). Trials carried out on cotrimoxazole prophylaxis shows that it reduces HIV-related morbidity, mortality and hospitalization, by decreasing the rates of developing opportunistic infections in people living with HIV and AIDS (8). The key benefit of cotrimoxazole prophylaxis is the reduction of the incidence of serious and often fatal Pneumocystis pneumonia (PCP). It also offers a high level of protection against toxoplasmosis, bacterial infections, diarrhea and malaria (32,33).

Kenya is one of the HIV 'high burden' countries in Africa with about 1.6 million people living with HIV infection at the end of 2016 (34). This has led to an increase in antibiotics use both for prophylaxis of opportunistic infections and treatment of comorbidities such as tuberculosis (TB). Thus, the high burden of HIV/AIDS in sub-Saharan Africa, Kenya included, implies increased risk of cotrimoxazole-linked ADRs (1,8).

Cotrimoxazole, a widely available and inexpensive antibiotic, is active against a variety of bacterial (gram positive and gram negative), fungal and protozoan infections. Cotrimoxazole has also been widely used as a treatment for common infections in many resource limited areas in HIV negative patients. The most common ADRs due to this group of drugs are skin reactions, from benign rash to potentially lethal Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Other ADRs include, GIT disturbance, headache, anaemia (prevented by folate supplementation), jaundice, photosensitivity, acute liver injury and pulmonary reactions (35).

2.2.5. Adverse drug reactions due to anti-tuberculosis drugs

In Kenya, tuberculosis treatment regimens have been standardized by the National Tuberculosis, Leprosy and Lung Disease (NTLD) program. The treatment recommended for all new cases of pulmonary and extrapulmonary tuberculosis, is the use of rifampin, isoniazid, pyrazinamide, and ethambutol for two months and, in the second phase, a combination of isoniazid and rifampin for another four months (2RHZE/4RH regimen). The treatment of all cases of recurrence and retreatment due to noncompliance, comprises of two months of streptomycin, rifampin, isoniazid, pyrazinamide, and ethambutol. This is followed by one month of rifampin, isoniazid, pyrazinamide, and ethambutol, and finally five months of rifampin, isoniazid, and ethambutol (2SRHZE/1RHZE/5RHE) (36).

Multidrug-resistant tuberculosis (MDR TB) poses difficulties in diagnosis and treatment, including increased occurrence of adverse reactions to antituberculosis (anti-TB) drugs, which affects the effectiveness of treatment. This is further complicated in the treatment of patients co-infected with HIV who are on antiretroviral therapy. Drugs used in the treatment of MRD TB include ethambutol, pyrazinamide, fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin) cycloserine, ethionamide, p-aminosalicylic acid, prothionamide and aminoglycosides (streptomycin, kanamycin, amikacin) (36,37). There are plans, however to change TB treatment guidelines in Kenya.

In 2015, a survey was carried out by the national TB program in Kenya to determine the prevalence of TB in the country. The study revealed that there are 558 people with TB among 100,000 people (38). Studies suggest that more than 15% of patients on anti-TB medication develop ADRs. Compared with patients without ADRs, patients with ADRs are more likely to have unsuccessful anti-TB outcomes (39).

The most frequent ADRs associated with drugs used in the treatment of TB include GIT reactions, liver dysfunction, ototoxicity, peripheral neuropathy, psychiatric disturbance, liver dysfunction, arthralgia, allergic reactions, neurological system disorders and renal impairment. ADRs are one of the major causes of non-adherence to anti-TB treatment (39).

2.2.6. Adverse drug reactions due to nitroimidazoles

Nitroimidazole derivatives are used for treatment of both bacterial infections (e.g pelvic inflammatory disease, *H. Pylori* infection, acute gingivitis) and protozoal infections (e.g. Giardiasis, amoebiasis, trichomoniasis). The adverse drug reactions include gastrointestinal tract symptoms such as nausea, anorexia, vomiting and metallic or bitter taste. Dizziness, urticarial, ataxia and headache have been reported. When given together with alcohol, a disulfiram-like intolerance reaction (manifesting as nausea, vomiting, headache, increased blood pressure, flushing, and shortness of breath) can be experienced (40,41). Drugs in this class include metronidazole, tinidazole and ornidazole.

A summary of serious adverse drug reactions due to the various classes of antibiotics is given in appendix III.

2.3. Risk factors associated with antibiotic adverse reactions

Factors that appear to increase the likelihood of experiencing an ADR include a history of ADRs, age, gender, concurrent illnesses, genetic predisposition, and drug-associated factors such as the specific kind of drug, route of administration, length of drug exposure, as well as the dose used. In addition, other risk factors linked with ADRs are multiple medications, length of hospital admission and physiological activity of excreting organs (42).

Recognition of these risk factors and the preventable ADRs is important in developing preventive to safeguard patients from preventable ADRs. The understanding of risk factors of adverse reactions will aid clinicians in identifying patients with an increased risk of developing adverse reactions and who may further gain from ADRs monitoring and reporting programs (43).

2.3.1. Past experience of antibiotic adverse drug reaction

A key influence in experiencing an adverse drug reaction is having had a past episode of the ADR. Repeated therapy with the same antibiotic as a result of poor documentation may lead

to the patient developing a similar ADR. Hence, reiterating the importance of careful and proper documentation of ADR when it occurs and sharing the pertinent details with the user will aid in averting its recurrence (44).

2.3.2. Antibiotic adverse reactions in the elderly

There are some special factors that concern antibiotic use in older patients which put them in danger of developing ADRs. Some cases of ADRs associated with antibiotic use which seem to develop to a greater extent in the older patients comprise: nephrotoxicity and ototoxicity due to aminoglycosides, pseudomembranous colitis, trimethoprims and sulfamethoxazale-induced blood dyscrasias, quinolone-linked seizures, doxycycline- associated esophageal ulcers and strictures, and acute liver injury due to chronic treatment with amoxicillin and clavulanic acid. *Clostridium difficile* associated with use of broad spectrum antibiotics mainly affects older people and leading to prolonged hospitalization, morbidity and mortality (45,46).

Normal physiology diminishes in kidney function due to advanced age predisposing older patients to a danger of toxicity due to the antibiotics. Older patients also suffer from multiple chronic illnesses and as a result use several drugs. Including an antibiotic to the patient's treatment presents additional risk for a drug-drug interaction. Judicious choice of the medicines to use, in addition to clinical and laboratory monitoring is therefore very crucial (45).

2.3.3. Antibiotic adverse reactions in children

Information concerning the occurrence, seriousness and the kind of drugs that more often cause adverse reactions in children is of concern. This is because clinical trials carried out before drug approval and market launch are carried out more often in adults. The safety profile of such medicines may differ markedly when the drug is consumed by children. An effective drug surveillance system is required to obtain data on medication hazards in the pediatric population (47).

In one study, the grouping of adverse drug reactions by Anatomical and Therapeutic Classification System revealed that antibiotics (67%) were the most frequent drug category associated with adverse reactions in children. Drugs most commonly implicated in ADRs were amoxicillin /clavulanate combination (21.87 %) followed by ceftriaxone (20.31 %). The

most commonly affected organ systems were skin and appendages, and the gastrointestinal system (47,48).

2.3.4. Antibiotic adverse reactions in pregnancy and lactation

Just as with the use of other drugs, the potential benefits of antibiotic therapy should be weighed against the risk to the unborn child. Some antibiotics have been determined to be teratogenic and ought to be totally avoided in the course of pregnancy. Examples include streptomycin and kanamycin (due to risk of hearing loss) and tetracycline (which may cause weakening, hypoplasia, and discoloration of long bones and teeth) (49).

2.4. Impact of antibiotic adverse drug reactions

Impact of ADRs due to antibiotics include the influence of ADRs on patient adherence to drug therapy, drug resistance, and treatment outcomes. Adverse drug reactions can cause significant morbidity and can occasionally lead to mortality. ADRs can complicate the management of diseases by impairing patient adherence to treatment (13). One study showed that 19% of patients on antibiotics did not finish their antibiotic course due of adverse reactions (50). Poor patient compliance to treatment can affect the effectiveness of treatment, leading to therapeutic failure and even antimicrobial resistance. Antimicrobial resistance may further cause severe illness, the use of more expensive drugs, drugs with a higher toxicity or less effective drugs, an increase in hospital admissions and increased mortality rates (51).

Though many of the ADRs may be moderate reactions, they result in a rise in health care expenditure because of hospitalization, a prolonged length of stay in hospital and require additional clinical investigations in serious cases, some medical interventions (1,52). A prolonged duration of illness and treatment, usually in a healthcare facility, increases health care costs and the economic burden on families and societies. Apart from the direct costs (costs related to facility expenses and treatment), indirect costs of adverse reactions, such as loss of productivity are also incurred (53).

Apart from the human costs linked with ADRs, these reactions have a considerable influence on public health systems. They inflict a major economic burden on the society and the already-stretched health-care systems. Apart from the economic impact, instances of adverse events affect the integrity of health system which may induce a loss of confidence of the public in the health system (54). Timely detection, assessment, monitoring and reporting of

ADRs are important to make drug therapy safe, efficient and cost effective. Educating the patients and healthcare workers may reduce the economic burden on the patient and on the health care system too (19,55).

2.5. Pharmacovigilance of antibiotics

Pharmacovigilance (PV) has been defined by the WHO as, "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems". The objectives of pharmacovigilance are to improve patient care and patient safety in regards to drug consumption. In addition, pharmacovigilance seeks to strengthen public health programs by contributing decisive, valid and crucial information for the proper assessment of the risk-benefit profile of drugs (56). Monitoring antibiotics use is pertinent because of the public health impact of adverse drug reactions, microbial resistance and public health expenditure (57).

In Kenya, the regulatory body Pharmacy and Poisons Board (PPB) has developed a national guideline on detecting and reporting ADRs. The objective of this guideline is to enable healthcare workers to contribute to the process of continuous surveillance of safety and efficacy of the pharmaceutical products, and therefore help to achieve its aim of making safer and more effective treatment available to patients (58).

Adverse reaction can occur with any class of drugs. According to one pharmacovigilance study, the most burdensome groups of medicines contributing to ADRs were antibiotics followed by antitumor agents, accounting for about 16% and 15% of cases, respectively (10). A different study showed that over 50% of all inpatients are put on antibiotic therapy and their use make up for 20–50% of medicine costs in health facilities. About 70% of patients get antibiotics for treatment or prophylaxis, with much of this use being empiric and over 50% of the recipients use multiple antibiotics (1).

2.5.1. Spontaneous reporting of adverse drug reactions

Spontaneous adverse drug reaction reporting is the backbone of PV. After medicines are available in the market for use by the general population, any new data on adverse reactions of medicinal products is almost solely initially revealed by spontaneous reporting (59). The objective of spontaneous reporting systems is to safeguard public health by issuing an initial warning system for hitherto unidentified dangerous ADRs. A driving force of these systems

is the notion of probable causality between ADRs and medicines, which then prompts the reporter, mostly a healthcare worker to spontaneously report an ADR (60,61).

When a healthcare worker suspects the occurrence of an ADR, they are encouraged to complete an individual case safety report (ICSR) and alert the country's drug regulatory agency, the Pharmacy and Poisons Board in the case of Kenya, about the suspected ADR. The ICSR is locally known as the Suspected Adverse Drug Reaction Notification Form. In general the information collected includes patient details (e.g. age, gender, weight), details on the suspected medicine (e.g. dose, duration of treatment), description of suspected reaction including the ADRs' severity and outcome, the patient's medical history, and other concomitant drugs that the patient was taking (62). These ICSRs can be filled either manually at the reporting site or electronically and are then submitted to the PPB by post, or via the internet. The submitted ICSRs were used as the source of data in this study (63,64).

The contribution of healthcare workers to ADRs databases is very important and has encouraged continuing determination of the benefit-risk ratio of medicines. This may also provide information towards signal detection of unpredictable and rare ADRs initially unidentified during the clinical trials of a drug (65).

2.5.2. Causality assessment of adverse drug reactions

A fundamental issue in pharmacovigilance is that most of the reported cases deal with uncertain ADRs. Adverse reactions are hardly specific for a particular drug, diagnostic tests to confirm the reactions are normally absent and a rechallenge is hardly ever ethically approved. Moreover, it is a challenge to ascertain the causality of antibiotic associated ADR in our hospital setting where a large proportion of inpatients have comorbidities and/or concurrently receive multiple medicines (59).

In Kenya, the WHO-UMC assessment scale are used when reporting adverse drug reactions. ADRs due to antibiotics can be categorized as either certain, probable, possible, unclassifiable or unassessible.

Assessing causality of ADRs due to antibiotics however can be difficult. For instance antibiotics are the therapeutic agents most often associated with hepatotoxicity. There may be challenges in the diagnosis of antibiotic-induced drug induced liver injury (DILI), particularly because some cases occur long after the drug has been stopped. It is also clinically similar to

other causes of acute hepatitis. Assessment is further compounded in patients with multiple comorbidities and on multiple medications making it difficult to identify which specific agent is the cause of the adverse reaction (66,67). The WHO as well as Kenya's national pharmacovigilance centre however, advise healthcare workers to report an ADR even if one is unsure of the cause of the reaction. One only needs to be suspicious to report it.

2.6. Regulation of antibiotics

Regulatory authorities worldwide have the mandate of ensuring medicines used in their countries or regions are of good quality, safety and efficacy. If an adverse drug reaction is suspected after approval, several courses of action can be taken by the regulator and/or manufacturer to ensure patient safety. Regulatory action may include updating the product label with specific warnings, issuing a Direct Healthcare Professional Communication, and product withdrawal from the market in serious cases. Changes in the standard treatment guidelines where needful in case of major as well as reoccurring issues with ADRs can be enacted (68).

In basing delivery of health services to a public health approach, it is necessary to estimate and evaluate hazards associated with drug therapy, in a timely manner, to diminish the risk to public health and to maintain public trust in the system. For instance, it is vital to be aware of which adverse reactions can be experienced with specific treatments and the number of users likely to suffer from this ADR. This kind of quantitative information has an explicit effect on standard treatment guidelines, policies and practices (69).

In Kenya, the regulatory authority is the Pharmacy and Poisons Board, a government agency under the Ministry of Health. The PPB has several directorates, key among them the medicines and medical products evaluation directorate, Pharmacy practice, Pharmaceutical inspection directorate and the Pharmacovigilance and Medicines information directorate. The PPB evaluates and registers antibiotics to be used in the country. It carries out continuous monitoring of the quality of antibiotics through sampling and analyzing their quality as well as post-market surveillance. The national pharmacovigilance centre coordinates the reporting of ADRs due to antibiotics. Systems for communication and sharing PV information have been set up by the PPB, including a newsletter (Lifesaver) and an e-mail-based medicine safety information sharing system, E shot (63,64).

In the United States, ADR reporting was launched in 1969. The drug regulatory authority, Food Drug Administration (FDA), uses the surveillance database known as the Adverse Event Reporting System to determine drug safety issues of approved drugs in use (70). The FDA has instituted market removal of antibiotics, since the launch of PV. Six out of twenty six antibiotics were withdrawn due to safety concerns. All were fluoroquinolones approved in the 1990s including temafloxacin (approved in 1992 and withdrawn in the same year), sparfloxacin (1996-2001), alatrofloxacin (1997-2001), trovafloxacin (1997-2001), grepafloxacin (1997-1999), and gatifloxacin (1999-2006) (71). Though these antibiotics were withdrawn in the USA, some of them were not withdrawn worldwide and may still be in use in other parts of the world. Gatifloxacin for instance, is still registered in Kenya by the PPB.

In the European Union (EU), the European Medicines Agency (EMA) began operating in 1995. The Agency coordinates pharmacovigilance in the EU using EudraVigilance, the system for managing and analyzing information on suspected ADRs (72).

There is need to study and document the burden of antibiotic-related ADRs in Kenya. This will aid healthcare workers develop measures targeted at minimize the potentially negative impact of these reactions.

CHAPTER THREE: METHODOLOGY

3.1. Study Design

The study was a retrospective cross sectional study that analyzed Individual Case Safety Reports (ICSRs) of antibiotic ADRs reported between January 2010 and December 2015 to the Pharmacy and Poisons Board in Kenya. From the PPB records, data was obtained and analyzed to determine the proportion of reported ADRs that were due to antibiotics. All the ICSRs submitted to the PPB between January 2010 and December 2015 were retrieved. The ICSRs were classified according to the drug suspected to have caused the ADR. A pre-designed data collection tool was used to abstract data from the ICSRs associated with antibiotics. Information on the patient's biodata, the reported ADR, the suspected antibiotic, concurrent medication, severity of the reported ADR, outcome of the ADR and causality assessment were abstracted.

3.2. Study Site

The study was carried out at Pharmacy and Poisons Board (PPB) in Nairobi, Kenya. This site was chosen because all ICSRs are submitted to this body and therefore an appropriate sample size could be obtained. The PPB is the drug regulatory authority in Kenya, instituted under the Pharmacy and Poisons Act, Chapter 244 of the Laws of Kenya. It is mandated to regulate the practice of pharmacy and the manufacture and trade in drugs and poisons. The Department of Pharmacovigilance was created in 2004 at the PPB with a mission to establish, enact and constantly improve an appropriate system for identifying, reporting and monitoring adverse drug reactions and other safety issues with drugs in Kenya. The National Pharmacovigilance System in Kenya was formally launched in 2009. Kenya was admitted as the 98th member of the World Health Organization (WHO) Program for International Drug Monitoring (PIDM) in 2010.The WHO PIDM member states submit reports of adverse reactions associated with medicinal products, known as Individual Case Safety Reports to the WHO global database, VigiBase. VigiBase is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (UMC).

Initially, ADR reports had to be filled manually at the site of reporting and submitted via post to the Board. The Pharmacovigilance electronic reporting system was then developed and

launched in 2013. It is an online reporting system where health workers log in and report in real time from their stations.

3.3. Study population

The study population consisted of all patients that experienced an adverse drug reaction due to an antibiotic for the period between January 2010 and December 2015 and whose cases were reported through the spontaneous ADR reporting system to the Pharmacovigilance department at the PPB. Reports included those submitted using both the Suspected Adverse Drug Reaction Reporting Form (PV 1) and the Pharmacovigilance Electronic Reporting System (PV-ERS).

3.3.1. Inclusion and exclusion Criteria

ICSRs were included in the study if they were submitted to the PPB during the study period between January, 2010 and December, 2015 and if the ADR reported was associated with antibiotic use. ICSRs submitted by healthcare workers and the general public were included in the study. ICSRs with missing information such as gender, age, and specific ADR were included in the study. However the missing information was noted during data analysis.

Individual Case Safety Reports were excluded from the study if they were physically damaged or otherwise illegible.

3.4. Sample size determination and sampling technique

The Guidelines for the National Pharmacovigilance system in Kenya direct that all suspected adverse reactions to conventional medicines, alternative medicines, medical devices and cosmetics should be reported. Universal sampling was used because very large sample sizes are normally required to detect rare adverse drug reactions. A pilot had been conducted before the study to determine the number of antibiotic associated ICSRs submitted during the review period and this informed the sampling technique that was used. All the cases that meet the study criteria was included in the study. From the PPB database, there were about 572 ICSRs associated with antibiotics submitted in the period between January 2010 and December 2015. Out of these, all the reports that met the inclusion criteria were analyzed.

3.5. Data collection procedures and instruments

A pre-designed data collection form adopted from the suspected adverse drug reaction reporting form (PV 1) was used to collect data.

Information on the patients' biodata, diagnosis, description of the ADR, details of the suspected drug, concomitant medicines used, severity of the reaction, outcome of the reaction and causality assessment were obtained from the ICSRs.

Data was abstracted retrospectively from both manually filed and computerized reports.

Information on documented regulatory action taken by PPB for the period January 2010 to December 2015 as a result of the spontaneous reports due to antibiotics was obtained from the board's records.

3.6. Variables and definitions

The predictor variables were age, sex, allergies, the antibiotic type and concurrent drugs.

The outcome variables of interest in this study were the type of ADR due to antibiotics, severity of the reported ADRs, recovery, inpatient hospitalization or prolongation of existing hospitalization, disability, congenital abnormalities and death.

Criteria for assessment of severity of an ADR was as described in the PPB ADR reporting form as follows:

A ***mild*** ADR required no change in treatment with the suspected drug or the ADR required that the suspected drug be withdrawn, discontinued or otherwise changed. No antidote was required and there was no increase in length of stay.

A ***moderate*** ADR required that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment was administered. The ADR caused an increased length of stay by at least one day or it was the reason for the hospital admission.

A ***severe*** ADR required intensive medical care and may have caused permanent harm to the patient.

A ***fatal*** ADR either directly or indirectly led to death of the patient.

The WHO-UMC causality assessment scale is used to assess causality. This is a system developed in consultation with the National Centres participating in the Programme for International Drug Monitoring to aid in a structured and harmonised assessment of causality.

It is a practical tool for the estimation of relationship likelihood between the suspected drug and the reported ADR. The causality categories used are certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable. This method gives guidance to the general arguments which should be used to select one category over another.

3.7. Data management

The collected data was keyed into Epi Info version 7 database and counterchecked for any double entries and errors. This data was backed up in an external hard disk for subsequent data analysis. Access to the folders containing the data was controlled by a password known only to the researcher.

3.8. Data analysis

Data analysis was performed using Stata version 13 software. Descriptive data analysis was carried out on all variables. The continuous variables were summarized either as mean and standard deviation or median and interquartile range (IQR). The categorical variables were reported as proportions using percentages. Bivariate analysis and logistic regression were conducted to determine the risk factors associated with severity and outcomes of antibiotic related adverse reactions. The association between severity and outcomes of ADRs and predictor variables was assessed at 95% confidence interval (CI). A P value of ≤ 0.05 was regarded as statistically significant. The numerator for prevalence was the number of submitted ICSRs that were associated with antibiotic use, whereas the denominator was the total number of ICSRs submitted during the study period. The regulatory actions taken by PPB in the five year period were summarized.

3.9. Ethical Considerations

Ethical approval was obtained from the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (Ref: KNH-ERC/RR/895). The approval letter from the ethics committee is attached in Appendix IX. Approval to collect data was obtained from the Pharmacy and Poisons Board (PPB/DBS/HR/GEN/Vol. 1/17/003). The approval letter from the board is attached in Appendix X.

Utmost care was taken to ensure the information obtained from the submitted ICSRs remained confidential. This was done by keeping the data collection forms under lock and key in a secure place accessible only to the researcher and assigning each ICSR a code instead of using patient's identifiers. The folders containing the softcopy of the data were secured by a password known only to the researcher.

CHAPTER FOUR: RESULTS

4.1. Prevalence of reported adverse drug reactions due to antibiotics

A total of 8852 Individual Case Safety Reports were submitted to the Pharmacy and poisons Board between January 2010 and December 2015, of which, 572 (6.46%) ICSRs were associated with antibiotic use.

The distribution of ICSRs on ADRs associated with antibiotics received at the PPB has been shown in Figure 4.1. In this analysis, twenty two (22) cases have been excluded because the ICSRs could not be traced at the PPB database.

Most of the ICSRs (179, 32.6%) were submitted in year 2013, while 105 (19.1%) and 125 (22.7%) reports were submitted in 2012 and 2014 respectively (Table 4.1). The increase in the reporting antibiotic related ADRs in 2013 might be attributed to the launch of electronic reporting of ADRs in that year.

Table 4.1: Submitted ICSRs due to antibiotics (2010-2015)

Year	No. of ICSRs submitted, n (%)
2010	14 (2.6)
2011	35 (6.4)
2012	105 (19.1)
2013	179 (32.6)
2014	125 (22.7)
2015	92 (16.7)

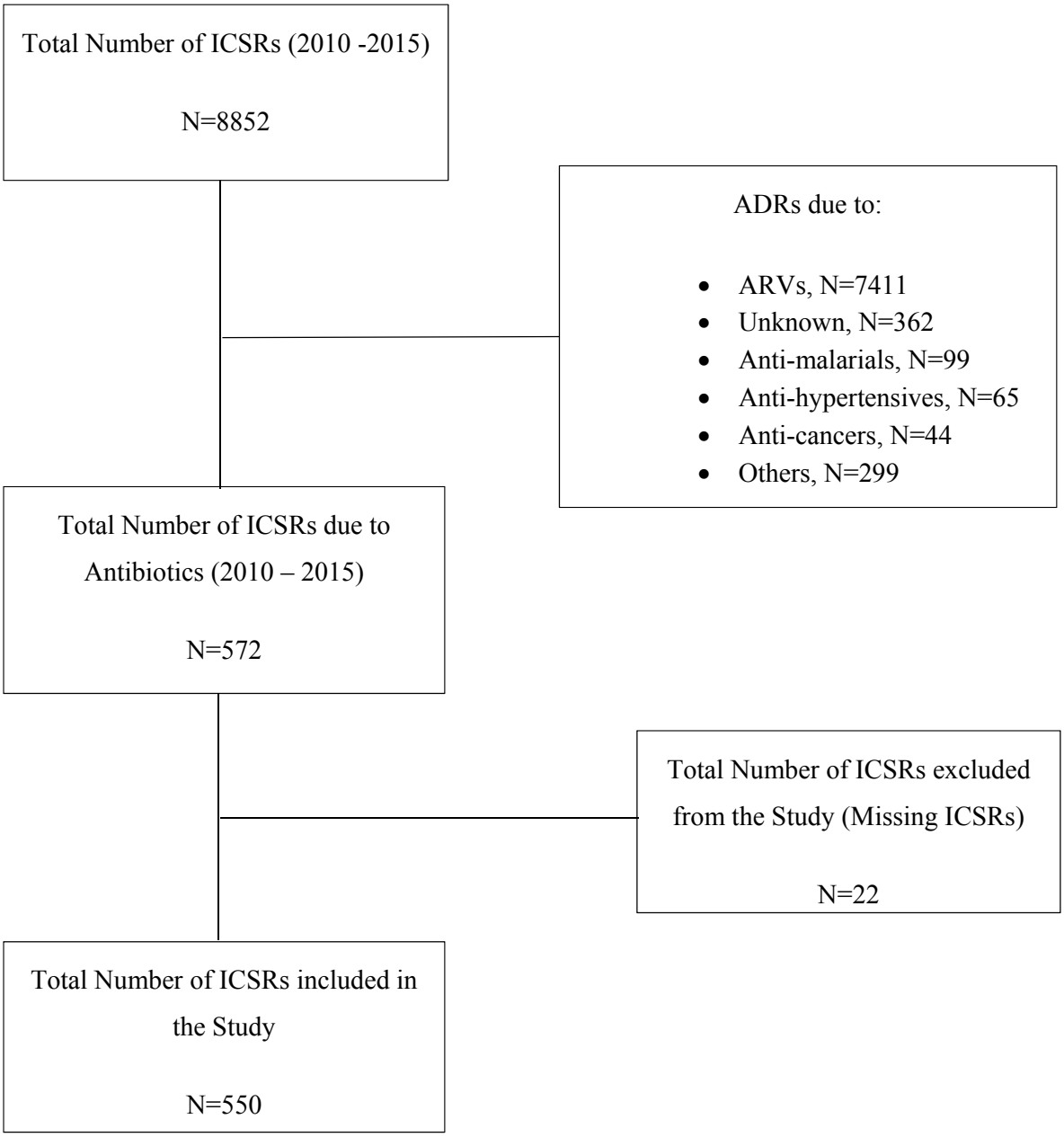


Figure 4.1: Flowchart of ICSRs analysed in this study from the PPB database (2010-2015)

4.2. Baseline characteristics of study subjects with reported ADRs due to antibiotics

The six year retrospective study revealed that female cases (330, 62.3%) predominated over males (200, 37.7%) in ADR occurrence**.** From the 416 participants whose ages were provided, it was found that the median age was 34.0 [IQR 22.0-45.0] years.

The main age group affected by adverse drug reaction in the present study was the 25-34 year age group (97, 17.6%) followed by those aged 35-44 years (96, 17.5%). Low occurrence of ADRs was apparent among those at the extreme end of the age spectrum. About 62 (11.3%) ADRs were reported in children under 15 years while 4 (0.7%) ADRs were reported in 75 years and above. The baseline characteristics of study subjects with reported ADRs due to antibiotics are summarized in Table 4.2.

Table 4.2: Baseline characteristics of study subjects with reported adverse drug reactions (n=550)

Characteristic	n (%)
Gender	
Male	200 (36.6)
Female	330 (60.0)
Not specified	20 (3.6)
Median Age [IQR]	34.0 [22.0-45.0]
Age groups	
<14	62 (11.3)
15 -24	56 (10.2)
25-34	97 (17.6)
35-44	96 (17.5)
45-54	61 (11.1)
55-64	29 (5.3)
65-74	11 (2.0)
75+	4 (0.7)
Not Specified	134 (24.4)
HIV Status	
Positive	306 (55.6)
Negative	244 (44.4)
ARV Use	
Yes	194 (35.3)
No	356 (65.7)
Indication for antibiotic use	
OI Prophylaxis	246 (46.5)
TB	84 (15.9)
URTI	47 (8.9)
IPT	21 (3.8)
Pneumonia	18 (3.4)
Others	113 (20.6)
Not specified	21 (3.8)

*OI-Opportunistic infections, TB-Tuberculosis, URTI-upper respiratory tract infection, IPT-isoniazid preventive therapy

4.3. Types of adverse drug reactions experienced by study subjects

Some study subjects had more than one reported ADR. There were many adverse drug reaction reported with the most frequently reported being skin rash (253, 39.7%), followed by

Steven-Johnson Syndrome (39, 6.1%), oral ulcers (37, 5.8%) and pruritus (37, 5.8%) as shown in Table 4.3. The ten leading ADRs account for about 70% of all ADRs reported.

Table 4.3: Types of adverse drug reactions experienced by study subjects

ADR	n (%)
Skin rash	253 (39.7)
SJS	39 (6.1)
Oral ulcers	37 (5.8)
Pruritus	37 (5.8)
Hepatotoxicity	35 (5.5)
Skin hyperpigmentation	29 (4.6)
Dizziness	13 (2.0)
Others*	194 (30.5)
TOTAL	**637 (100)**

SJS-Steven-Johnson Syndrome

*A complete list of reported ADRs is shown in Appendix IV

4.4. Site and organ systems affected by reported adverse drug reactions

The ADRs were further analyzed by site of occurrence. The organ systems most commonly affected by the adverse drug reaction were the Integumentary system (388, 60.9%),) the gastrointestinal tract system (75, 11.8%) and the central and peripheral nervous system (72, 11.3% as shown in Table 4.4.

Table 4.4: Site of reported adverse drug reaction from PPB database by organ system

SITE OF ADR	No. of cases, n (%)
Integumentary system	388 (60.9%)
Gastrointestinal tract system	75 (11.8%)
Central and peripheral nervous system	72 (11.3%)
Endocrine system	41 (6.4%)
Others*	35 (5.4%)
Respiratory system	11 (1.7%)
Cardiovascular system	9 (1.4%)
Musculoskeletal system	8 (1.3%)
Reproductive system	3 (0.5%)
Total	**637 (100%)**

*A complete list of reported ADRs by organ system is shown in Appendix IV

4.5. Suspected antibiotic class causing reported adverse drug reaction

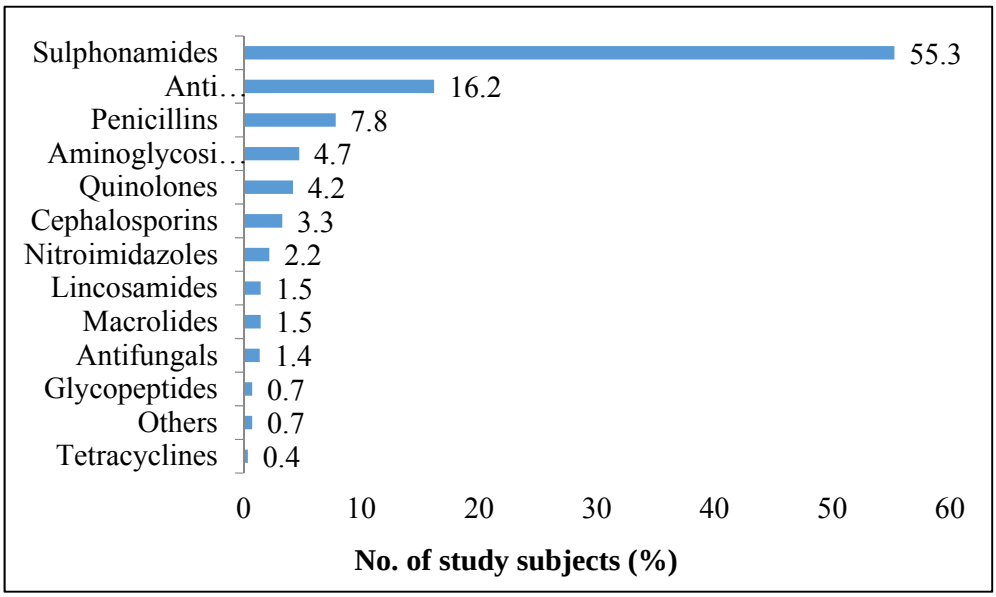
The most commonly reported antibiotic which caused adverse drug reactions during the period under review was cotrimoxazole (304, 55.3%) as shown in Table 4.5. Other important suspected drugs causing reported ADRs, were isoniazid (43, 7.8%), RHZE combination (16, 2.9%) and ciprofloxacin (15, 2.7%). The top 10 antibiotics accounted for about 80% of the reported ADRs.

Table 4.5: Suspected antibiotic causing reported adverse drug reactions from the PPB database

Suspected drug	n (%)
Cotrimoxazole	304 (55.3)
Isoniazid	43 (7.8)
RHZE	16 (2.9)
Ciprofloxacin	15 (2.7)
Rifampicin	12 (2.2)
Kanamycin	12 (2.2)
Amoxicillin	11 (2.0)
Benzyl penicillin	11 (2.0)
Streptomycin	11 (2.0)
Ceftriaxone	10 (1.8)
Others*	105 (19.1)

*A complete list of suspected antibiotics and antibiotic classes causing reported ADR is given in Appendix V

The antibiotics which were suspected to have caused the reported ADRs were clustered into antibiotic classes. The antibiotic class associated with the most number of reported adverse drug reactions was sulfonamides (304, 55.3%), followed by anti-tuberculosis agents (89, 16.2%) and penicillins (43, 7.8%) in that order. Aminoglycosides were responsible for 4.8% of the ADRs reported. All the other classes accounted for 26 (15.5%) of the ADRs. The summary of classes of drugs responsible for ADRs is presented in Figure 4.2.


Sulphonamides
Anti…
Penicillins
Aminoglycosi…
Quinolones
Cephalosporins
Nitroimidazoles
Lincosamides
Macrolides
Antifungals
Glycopeptides
Others
Tetracyclines
55.3
16.2
7.8
4.7
4.2
3.3
2.2
1.5
1.5
1.4
0.7
0.7
0.4
0
10
20
30
40
50
60
No. of study subjects (%)

4.5.1. Reported adverse drug reactions due to Sulphonamides

The Sulphonamide class of antibiotics was linked to the majority (304 cases, 55.3 %) of the reported ADRs. Cotrimoxazole (Sulfamethoxazole/Trimethoprim) was the only sulphonamide reported to have caused an ADR.

Out of the 304 study subjects with ADRs due to cotrimoxazole in this study, 242 (80.6%) subjects were HIV positive and were taking the drug for prophylaxis of opportunistic infections. The other 62 cases were HIV negative, of which 30 subjects (10%) were taking cotrimoxazole for treatment of upper respiratory tract infection.

Most

Figure 4.2: Class of antibiotics causing reported adverse drug reactions in study subjects

(197, 67.5%) of the ADRs associated with sulphonamides were experienced by females, and 95 (32.5%) by males. Most of the ADRs (252, 82.9%) were dermatological reactions with skin rash accounting for 163 (54.5%) of the total reactions as shown in Table 4.6.

Table 4.6: Summary of adverse drug reactions due to sulphonamides (n=304)

Characteristic	n (%)
Gender	
Female	197 (64.8)
Male	95 (31.5)
Not specified	12 (3.9)
Site of ADR	
Integumentary	252 (82.9)
GIT	30 (10.0)
CNS/PNS	5 (1.7)
Cardiovascular	4 (1.3)
Endocrine	3 (1.0)
Reproductive	2 (0.7)
Respiratory	2 (0.7)
Others*	1 (0.3)
Not specified	5 (1.6)
Type of ADR reported	
Skin rash	163 (54.5)
SJS	33 (11.0)
Oral ulcers	21 (6.9)
Skin hyperpigmentation	20 (6.7)
Pruritus	15 (5.0)
Others*	47 (15.5)
Not specified	5 (1.6)

*A complete list of ADRs due to sulphonamides is given in Appendix VI

4.5.2. Reported adverse drug reactions due to Anti-Tuberculosis agents

A total of 89 (16.2%) of the submitted reports were linked to the use of anti-tuberculosis drugs, accounting for the second most common antibiotic class causing the reported ADRs. Of the 89 cases reported, 63 (75%) were using the anti-tuberculosis agents for the treatment of TB, while 23 (25%) were on Isoniazid Prophylaxis Treatment (IPT). About 42 (50.0%) of the reported cases had moderate reactions while 31 (36.9%) cases had mild reactions (Table

4.7). About 10 (11.9%) cases had severe reactions and there was one case (1.12%) of fatality associated with use of rifampicin/ isoniazid/ pyrazinamide combination. Endocrine system accounted for 30 (27.0%) of the reported adverse reactions, with hepatotoxicity 30 (27.0%) being the most frequent reported ADR due to anti-TB agents. CNS/PNS adverse reactions also accounted for 30 (27.0%) of the reported reactions due to anti-TB drugs. About 21 (70.0%) cases of peripheral neuropathy and 5 (16.7%) cases of dizziness were reported as affecting the CNS/PNS system.

Table 4.7: Summary of adverse drug reactions due to Anti-Tuberculosis agents

Characteristic	**n (%)**
Gender	
Female	50 (56.2)
Male	34 (38.2)
Not specified	5 (5.6)
Total	**89**
Suspected drug	
Isoniazid	43 (48.3)
RHZE	16 (18.0)
Rifampicin	12 (13.5)
RHZ	9 (10.1)
Cycloserine	4 (4.5)
Pyrazinamide	3 (3.4)
Ethambutol	1 (1.1)
RHE	1 (1.1)
Total	**89**
Endocrine	30 (27.0)
CNS/PNS	30 (27.0)
Integumentary	14 (12.6)
GIT	13 (11.7)
Musculoskeletal	6 (5.4)
Reproductive	1 (0.9)
Cardiovascular	1 (0.9)
Others*	12 (9.0)
Total	**111**
ADR	
Hepatotoxicity	30 (27.0)
Peripheral neuropathy	21 (18.9)
Skin rash	12 (10.8)
Red colored urine	6 (5.4)
Dizziness	5 (4.5)
Oral ulcers	4 (3.6)
Others*	33 (29.7)
Total	**111**

RHZE - rifampicin/isomiazid/pyrazinamide/ethambutol, RHZ – rifampicin/isoniazid/pyrazinamide, RHE – rifampicin/isoniazid/ethambutol, CNS/PNS - central nervous system/peripheral nervous system, GIT - gastrointestinal tract.* A complete list of ADRs due to anti-TB agents is attached in Appendix VII

4.6. Types of concomitant drugs used together with antibiotics by study subjects

There were study subjects who were also on other concomitant medicines in addition to their respective antibiotic therapy. About 141 (35%) of these cases were on ARVs. A further 93 (23.1%) study subjects were on pain relievers while 74 (18.4%) were taking micronutrients. The classes of concomitant medicines has been summarized in Table 4.8. The specific medicines in each class are given in Appendix VIII.

Table 4.8: Classes of concommitant drugs used by the study subjects

Medication class	n (%)
ARVs	141 (35.0)
Pain relievers	93 (23.1)
Micronutrients	74 (18.4)
GIT-acting drugs	22 (5.5)
Antihypertensives	22 (5.5)
Antimalarials	19 (4.7)
Antihistamines	11 (2.7)
Antidiabetics	9 (2.2)
Others*	12 (3.0)

ARVs- anteretrovirals, GIT-gastrointestinal
*A complete list of concomitant drugs is given in Appendix VIII

4.7. Severity and Actions taken to manage reported adverse drug reactions

Out of the 550 analyzed reports, 533 (96.9%) reports indicated the level of severity of the reported ADRs. ‘Mild’ and ‘moderate’ reactions accounted for 170 (31.9%) and 270 (50.7%) cases respectively. Only 84 (15.8%) of the reactions were judged to be ‘severe’ while “fatal” reactions accounted for 8 (1.5%) cases. Sulphonamides were suspected to have caused most (49, 16.6%) the reactions classified as severe, followed by anti-TB agents (10, 11.9%). Antibiotics associated with the fatal cases were two cases of benzathine penicillin use that resulted in sudden death, and one case each of amoxicillin/clavulanic acid (SJS), kanamycin (nephrotoxicity), RHZ (hepatotoxicity), ciprofloxacin (respiratory distress), levofloxacin (SJS) and cotrimoxazole (SJS). Five of the fatal cases were female and three were male.

One (0.2%) case was indicated as having unknown severity despite a clear guide on how to assess severity on the reporting form. Figure 4.3 illustrates the distribution of ADR cases due to antibiotics by their severity.

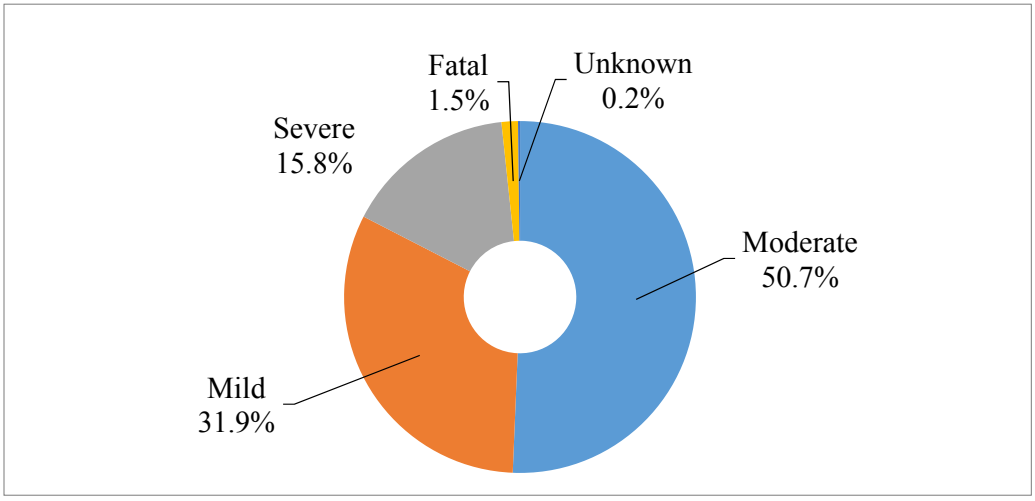


Figure 4.3: Severity of reported adverse drug reactions in the study subjects

Table 4.9 shows the actions taken to manage the reported ADRs. Most of the ADR were managed by withdrawing the suspected medicine (435, 79.1%). In other 67 cases (12.2%), the dose was not changed while action was unknown in only 3 (0.5%) cases.

Table 4.9: Distribution of cases by Action Taken

Action taken	**n (%)**
Drug withdrawn	435 (79.1)
Dose not changed	67 (12.2)
Dose reduced	17 (3.1)
Unknown	3 (0.5)
Dose increased	1 (0.2)
Not Specified	27 (4.9)
Total	550

Table 4.10 shows a cross-tabulation of cases by severity of reaction and action taken. Although most of the cases were mild and moderate in nature, the suspected drug was withdrawn in 124 (74.7%) and 225 (85.9%) of the cases respectively.

Table 4.10: Distribution of cases by severity of reaction and action taken

Severity of Reaction	Action Taken						Total
	Drug Withdrawn	Dose Not Changed	Dose Reduced	Drug Increased	Unknown	Not specified	
Mild	124	39	3	0	0	4	170
Moderate	225	22	11	1	3	8	270
Severe	75	5	2	0	0	2	84
Fatal						8	8
Unknown	1	0	0	0	0		1
Not Specified	10	1	1			5	17
Total	**435**	**67**	**17**	**1**	**3**	**27**	**550**

4.8. Outcomes of reported adverse drug reactions due to antibiotics in study subjects

Majority of the study subjects (143, 42.5%) reported complete recovery, while 213 (28.5%) cases were in the process of recovering at the time of reporting the ADR. About 31 (6.2%) cases required an intervention to prevent permanent damage. Ten (2.0%) cases required hospitalization and 14 (2.8%) cases were reported as not recovered with eight of them having died as a result of the ADR. The outcome of 90 cases (18.0%) was unknown. Figure 4.4

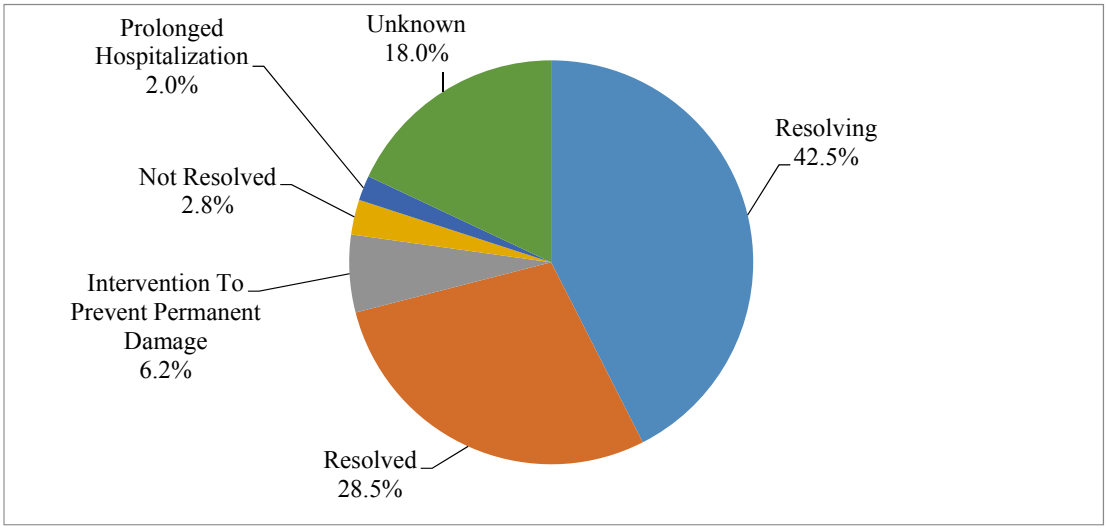


Figure 4.4: Distribution of outcomes of reported adverse drug reactions in study subjects

shows the outcome of the reported ADRs.

4.9. Assessment of causality of reported adverse drug reactions

The reported ADRs were assessed using the WHO-UMC causality assessment scale, which categorizes the causality into certain, probable, possible, unassessable/unclassifiable, unlikely and conditional / unclassified. Analysis showed that two thirds (311, 66.2%) of the reported ADRs were categorized as probable/likely, 86 (18.3%) as certain and 52 (11.1%) as possible (Table 4.11).

Table 4.11: Assessment of causality of reported adverse drug reactions

CAUSALITY	**n (%)**
Probable/Likely	311 (66.2)
Certain	86 (18.3)
Possible	52 (11.1)
Unassessable/ Unclassifiable	10 (2.1)
Unlikely	9 (1.9)
Conditional/Unclassified	2 (0.4)
Total	470

A total of 66 (12%) reported ADRs had more than one drug associated with their occurrence, with nevirapine accounting for 34 (54.6%) of these cases. These medicines were reported since the reporter was not able to determine whether the ADR was caused by the antibiotic alone or by the concomitant drugs due to a similarity in their ADR profiles. A list of the other suspected drugs is shown in Table 4.12. There were more than one antibiotic suspected of having caused the reported ADR in 7 study subjects.

Table 4.12: Concomitantly used drugs suspected to have caused the reported ADRs

Other concomitantly used drugs suspected to have caused reported ADRs	n (%)
Nevirapine	36 (54.6)
Efavirenz	6 (9.1)
Cotrimoxazole	3 (4.6)
Ceftriaxone	2 (3.0)
Lamivudine	2 (3.0)
Levofloxacin	2 (3.0)
Tenofovir	2 (3.0)
Others*	13 (19.7)
Total	66 (100)

*One case each of abacavir, artemether/lumefantrine, amoxicillin/clavulanic acid, cefuroxime, diclofenac, ethambutol, ibuprofen, kanamycin, omeprazole, prothionamide, rifampicin, streptomycin and metronidazole.

4.10. Factors associated with severity of reported adverse drug reactions

Bivariate analysis was conducted to determine the factors associated with severity of ADRs reported in ICSRs.

Age was one of the factors in determining the severity of the adverse drug reaction. As age of the study subjects increased, the odds of developing severe or fatal reactions decreased compared to children aged 0-14 years (Table 4.13). The odds of having severe or fatal reactions increased again with the elderly (75-88 years). Though other factors such as gender, HIV status, ARV use and the number of ADRs experienced were important, they were not significantly associated with severity of ADRs in the study subjects.

Table 4.13: Bivariate Analysis of factors associated with severity of ADRs (N=512)

Variable	Mild/ Moderate n (%)	Severe & Fatal n (%)	Odds ratio	p-value
Gender				
Female	264 (82.8)	55 (17.2)		
Male	156(80.8)	37(19.2)	1.139 (0.718-1.806)	0.582
Age group				
0- 14	41 (70.7)	17(29.3)		Ref
15 -24	45 (79.0)	10(21.0)	0.536 (0.230-1.303)	0.166
25-34	79 (87.2)	16 (12.8)	0.489 (0.224-1.066)	0.069
35-44	78 (90.3)	13 (9.7)	0.402 (0.178-0.908)	**0.025**
45-54	53 (80.0)	6 (20.0)	0.273 (0.099-0.754)	**0.009**
55-64	26 (5.9	3 (3.3)	0.278 (0.07-1.094)	**0.047**
65-74	11 (2.5)	0 (0.0)	0	**0.003**
75-88	3 (0.7)	1 (1.1)	0.804 (0.078-8.286)	0.854
Not specified	10 (423.6)	26 (28.3)		
HIV Status				
Negative	194(81.9)	43(18.1)		
Positive	246(83.4)	49(16.6)	0.899 (0.572-1.410)	0.642
Concomitant ARV use				
No	286(82.9)	59(17.1)		
Yes	154(82.4)	33(17.6)	1.039 (0.650-1.660)	0.874
No. of ADRs				
1	375(83.1)	76(16.9)	Ref	
2	46(82.1)	10(17.9)	1.073 (0.519 - 2.219)	0.850
3 & Over	15(71.4)	6(28.6)	1.974 (0.742 - 5.250)	0.166

4.11. Factors associated with outcomes of reported adverse drug reactions due to antibiotics

One of the key aims of the study was to assess the association between outcomes of ADRs and the various predictor variables such as gender, age group, HIV status, ARV use and the number of ADRs experienced. Of all the factors examined, the HIV status of the study

subjects and the severity of reported ADRs were significantly associated with the outcomes of reported ADRs (Table 4.14).

HIV positive study subjects had twice the odds of having not recovered from the reported ADRs compared to the HIV negative study subjects (OR=2.1, p=0.011).

Study subjects who had severe/fatal level of ADR severity had more than three times the odds of not recovering from the reported ADRs compared to those who reported mild/moderate ADRs (OR=2.0, p<0.001).

4.12. Regulatory action taken by PPB due to antibiotic related ADRs

Kenya is a member of the WHO-Programme for International Drug Monitoring. The PPB therefore submits individual case safety reports to VigiBase, the WHO global ICSR database. Due to the low number of ICSRs submitted to the national database, it is not possible to carry out data mining. The board disseminates relevant regulatory actions that it has taken through a newsletter (Lifesaver) and an e-mail-based medicine safety information sharing system, E shot. During the study period, the PPB updated recommendations concerning the interaction of ceftriaxone with calcium-containing products. This was as a result of previously reported fatal cases in neonates and subsequent US FDA recommendations based on 2 studies carried out by the manufacturer

Table 4.14: Bivariate Analysis of Factors associated with Outcome of adverse drug reactions (N=411)

	Recovered/ Recovering (n, %)	Not Recovered (n, %)	Odds ratio	P-value
Gender				
Female	209 (87.4)	30 (12.6)		
Male	136 (86.6)	21(13.4)	1.0757 (0.5916 - 1.9562)	0.8108
Not specified	11 (73.3)	4 (26.7)		
Age group				
0- 14	44 (88.0)	6 (12.0)		
15 -24	64 (83.1)	13 (16.9)	1.490 (0.526-4.217)	0.451
25-34	90 (88.3)	12 (11.7)	0.978 (0.344-2.778)	0.966
35-44	67 (87.0)	10 (13.0)	1.09 (0.371-3.227)	0.870
45-54	91 (86.7)	14 (13.3)	1.128 (0.906-3.135)	0.817
55-64	23 (92.0)	2 (8.0)	0.638 (0.119-3.414)	0.597
65-74	7 (87.5)	1 (12.5)	1.048 (0.109-10.063	0.968
75-88	3 (75.0)	1 (25.0)	2.111 (0.218-27.452)	0.456
Not specified	91 (86.7)	14 (13.3)		
Concomitant ARV use				
No	184 (88.9)	23 (11.1)		
Yes	172 (84.3)	32 (15.7)	1.488 (0.838-2.644)	0.173
HIV STATUS				
Negative	255 (88.9)	30 (11.1)		
Positive	101 (84.3)	25 (15.7)	2.104 (1.180-3.753)	**0.011**
No. ADR				
1	297 (86.3)	47(13.7)		
2& Over	61 (88.9)	16(11.1)	1.294 (0.708-2.366)	0.401
Severity of ADR				
Mild/ Moderate	293	32		
Severe/ Fatal	57	15	2.015 (1.226-4.736)	**0.009**

Further analysis using logistic regression was undertaken. Table 4.15 summarizes the importance of the two explanatory variables individually whilst controlling for the other explanatory variables.

The HIV negative study subjects had 0.65 odds of not recovering or having an undesirable outcome compared to the HIV positive study subjects. It is seen that the test for the variable HIV status (OR = 0.650, p=0.149) is not significant. This means that although there was an association between outcome versus HIV status of the subjects and the outcome of the reported ADR, once the other variables were controlled for, there is not a strong enough relationship between HIV variable and outcome.

Study subjects with ADRs of Mild/Moderate severity had a lower odds (OR=0.279, p<0.001) of not recovering compared to those with Severe/ Fatal severity.

Table 4.15: Multivariate Analysis for independent variables of outcomes

Variable	Coefficient	Standard Error of Coefficient	Odds Ratio (95.0% Confidence Interval)	p value
HIV Status	-0.431	0.299	0.650 (0.362 - 1.167)	0.149
Severity of ADR	-1.277	0.309	0.279 (0.152 - 0.511)	**<0.001**

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1. Discussion

The aim of this study was to describe the prevalence and characteristics of reported adverse drug reactions due to antibiotics by evaluating the Individual Case Safety Reports at the PPB for the period January 2010 to December 2015.

A key finding was that skin reactions were the most common ADR reported. Skin reactions accounted for 60.9% of all the reported reactions with the most common being skin rash (253, 39.7%). This was followed by the GIT system (11.8%) and the central and peripheral nervous systems (11.3%). The results are consistent with the study carried out by Bharathi *et al*. in 2008 (73) which showed that the organ systems most commonly affected by ADRs were integumentary (61.6%), renal and gastrointestinal system (13.7%) and CNS (11%).

The overall prevalence of ICSRs submitted to the PPB that were associated with antibiotics was 6.46%, second to those associated with ARVs use which accounted for 83.7% of all submitted ICSRs during the period of interest. The prevalence of antibiotic ADRs in this study was comparatively lower than 41% reported in Uganda (67) and 31.91% reported in India (6). This difference could be attributed to more focus that is put on ARV monitoring as compared to antibiotic monitoring in Kenya, including setting up of Antiretroviral Therapy ADR sentinel surveillance sites. Further, the other two studies were prospective studies where health care professionals actively monitored for any ADR. This is in contrast with this present study where spontaneously reported ADRs were analyzed. This is a passive method of ADR reporting. This might explain the high prevalence of ADRs due to antibiotics in the previous studies.

Females were found to have a higher frequency of reported ADRs (330, 62.3%) compared to males ((200, 37.7%)). This was consistent with other studies that found that women are 50 to 75 percent more likely than men to experience an adverse drug reaction (74). Physiological differences between men and women may contribute to this difference, including pharmacokinetic and pharmacodynamics differences. For instance, women have a lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate (74).

In addition, sulphonamides, specifically cotrimoxazole, were found to cause most of the reported ADRs. Cotrimoxazole (304, 55.3%) was the antibiotic most frequently linked to the reported ADRs. This finding is comparable to a study carried out in the US that found that sulfonamides accounted for the highest cases of hospital visits due to ADRs (75). However, a study conducted in India (1) revealed the predominance of cephalosporins (34.69%) followed by aminoglycosides (23.01%), whereas beta-lactams (40.4%) and aminoglycosides (23.01%) accounted for majority of the ADRs in a different study conducted in India as well (19). 242 (80.6%) subjects who experienced adverse reactions due to cotrimoxazole were HIV positive. Cotrimoxazole is the standard of care for HIV positive patients in Kenya for prophylaxis of opportunistic infections. This may contribute to the high frequency of ADRs associated with the drug. Females (197, 67.5%) reported more ADRs due to sulphonamides as compared to males (95, 32.5%). This may be because women (7.0% HIV prevalence) in Kenya are more vulnerable to HIV infections compared to men (4.7% HIV prevalence) and therefore there are more females on cotrimoxazole prophylaxis compared to males (32).

Anti-TB drugs accounted for the second most frequent cause of reported ADRs (89, 16.2%). In this study, it was not easy to correlate the reported adverse reaction with the drugs used in the treatment of tuberculosis. This is because many of the reactions (389, 42.7%) were experienced during treatment with a combination of two or more anti-TB drugs. This made it impossible to identify the specific drug that caused the reported adverse effects in most cases. This scenario was also noted in a study conducted in Brazil in 2008 (76). Among the ADRs caused by anti-TBs, liver dysfunction accounted for the majority (27%) of the cases. This was higher than the 3.8% reported in India (77) and 8.1% reported in Brazil (76). Risk factors for hepatotoxicity, such as alcohol abuse or use of other hepatotoxic drugs, can vary among the populations studied, which would explain the difference. The difference might also be explained by the different criteria for liver injury applied in the different studies.

Severity assessment showed that most of the reported cases were moderate (50.7%) followed by mild (31.9%) and severe (15.8%). This was comparable to findings of a study carried out in Taiwan which had 58.4% moderate cases (78). This shows that most cases (66.2%) required an intervention either in the form of treatment with an antidote, symptomatic treatment or hospitalization to manage the reported ADR. The mild cases did not require any treatment. Early recognition and diagnosis of antibiotic associated adverse reactions is key as these reactions are potentially life threatening. The mortality rate due to ADRs associated

with antibiotics was 1.5% in this study. This was lower than the 3% reported in a prospective study carried out in India in 2009 (73). This may have been due to a larger sample size in the India study.

This study showed that the HIV status of the study subjects was associated with outcomes of the reported adverse reactions. It found that a HIV positive status increased the risk of having undesirable outcomes including no recovery. This indicates that this category of patients require close monitoring and follow up as they continue with their treatment and during the management of antibiotic related ADRs.

Most of the reported cases (79.1%) had the offending antibiotic withdrawn. This resulted in a positive outcome where about 70% of the cases were reported to either have recovered or were in the process of recovering. This demonstrates that positive treatment outcomes can still be achieved in patients when appropriate management of ADRs is carried out.

Causality assessment by WHO scale revealed that 66.2% of the suspected antibiotics were probable/likely to have caused the reported ADR. This was comparable to 73.98% reported in India (78). About 18.3% of the antibiotics were assessed as certain to have caused the reported ADR. The rest (15.5%) ranged from possible to unclassifiable. This may be due to use of more than one drug concomitantly. The reporter may not have been able to distinguish which specific drug caused the observed ADR.

Kenya is a member of the WHO-Programme for International Drug Monitoring. The PPB therefore submits individual case safety reports to VigiBase, the WHO global ICSR database. The board disseminates relevant regulatory actions that it has taken through a newsletter (Lifesaver) and an e-mail-based medicine safety information sharing system, E shot. (63).

5.2. Conclusion

This study showed a high burden of antibiotic related morbidity and mortality in patients taking antibiotics. Due to the nature of the reported ADRs, majority of the cases required an intervention to manage them. Antibiotics were also suspected to have contributed to fatalities during the study period.

This study found that most of the reported ADRs affected the skin. Majority of the ADRs affected HIV positive patients on cotrimoxazole as a prophylaxis of opportunistic infections.

The HIV status of the patients also put them at risk of having undesirable outcomes, including no recovery.

The findings in this study emphasize the need for close monitoring and follow up of all patients especially HIV infected patients on antibiotics as well as children and the elderly who suffered from severe ADRs. The health care providers should make an attempt for early detections of ADRs and be vigilant about safety profile monitoring of antibiotics. This will not only decrease the morbidity and mortality but also the health care costs.

5.3. Recommendations

The health care providers should make an attempt to set up systems for early detections of ADRs and be vigilant about safety profile monitoring of the prescribed medicines. This will not only decrease the morbidity and mortality associated with antibiotics but also health care costs.

Further sensitization and training on ADR reporting healthcare workers should be done to improve the rate of ADR reporting due to antibiotics and to improve the quality of the submitted reports. According to the national pharmacovigilance guidelines, the PPB targets the general public as one source of pharamcovigilance data. The public should therefore be sensitized on reporting of ADRs. This study included only 2 reports submitted by the public.

Larger prospective studies are recommended to determine the true incidence of antibiotics related adverse reactions because the voluntary nature of the spontaneous reporting system may have underestimated the occurrence of these ADRs.

5.4. Strengths and limitations of the study

The use of the national database of ADRs, in this case the PPB, to look at ADRs patterns and their association with actions taken and their clinical outcome, usually enables the researcher to include larger patient samples robust enough to detect ADRs though sometimes at the cost of diminished quality of collected data. Some reports were not completely legible while some had incomplete data. It was also difficult to verify the reported information.

Given the voluntary nature of the reporting system, the extent of underreporting (and hence the actual prevalence) of ADRs due to antibiotics is difficult to determine.

Drug-drug interactions were not ruled out during analysis of the ADRs associated with antibiotics. These interactions may have been a possible cause of the observed adverse reactions.

5.5. Information dissemination plan

The findings of this study will be shared with PPB and disseminated through publications, sensitization of healthcare workers in scientific conferences and through conducting continuous medical education.

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APPENDICES

Appendix I: Data collection form

Patient Biodata

Patient study number ……

Date of birth ……

Age in years (at time of reporting ARD)……

Gender (female/male) ……

Weight…….

Location (county).....

Medication history

Diagnosis…….

Report date ……

Suspected drug……...

Other drug(s)……..

Description of ADR reaction

….……

Severity of reaction (tick where appropriate)

- □ Mild
- □ Moderate
- □ Severe
- □ Fatal
- □ Unknown

Action taken (tick where appropriate)

- Drug withdrawn
- Dose increased
- Dose reduced
- Dose not changed
- Unknown

Outcome (tick where appropriate)

- Recovering/resolving
- Recovered/resolved
- Requires or prolongs hospitalization
- Causes a congenital anomaly
- Requires intervention to prevent permanent damage
- Unknown

Reporter (designation)…….

Appendix II: Suspected Adverse Drug Reaction Reporting form

PV 1

MINISTRY OF HEALTH
THE PHARMACY AND POISONS BOARD
P. O. Box 27663-00506 NAIROBI
Tel: (020) 2716905 / 6 Ext 114 Fax: (020) 2713431/2713409
Email: pv@pharmacyboardkenya.org

IN CONFIDENCE

☐ Initial Report
☐ Follow-up Report

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

NAME OF INSTITUTION: _____ INSTITUTION CODE: _____

ADDRESS: _____ CONTACT: _____

PATIENT'S NAME/ INITIALS: _____ IP/OP. NO.: _____ D.O.B: _____

PATIENT'S ADDRESS: _____ WARD/CLINIC: _____ GENDER: ☐ Male ☐ Female

ANY KNOWN ALLERGY: ☐ No PREGNANCY STATUS: ☐ Not Pregnant WEIGHT (kg): _____
☐ Yes (specify): _____ ☐ 1st Trimester
☐ 2nd Trimester HEIGHT (cm): _____
☐ 3rd Trimester

DIAGNOSIS: (What was the patient treated for) _____

BRIEF DESCRIPTION OF REACTION: _____

LIST OF ALL DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals) (Use side of this form for additional drugs)	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (√) SUSPECTED DRUG(S)
1						
2						
3						
4						
5						

SEVERITY OF THE REACTION: (Refer to scale overleaf)
☐ Mild
☐ Moderate
☐ Severe
☐ Fatal
☐ Unknown

ACTION TAKEN:
☐ Drug withdrawn
☐ Dose increased
☐ Dose reduced
☐ Dose not changed
☐ Unknown

OUTCOME:
☐ Recovering / resolving
☐ Recovered / resolved
☐ Requires or prolongs hospitalization
☐ Causes a congenital anomaly
☐ Requires intervention to prevent permanent damage
☐ Unknown

CAUSALITY OF REACTION: (Refer to scale overleaf)
☐ Certain
☐ Probable / Likely
☐ Possible
☐ Unlikely
☐ Conditional / Unclassified
☐ Unassessable / Unclassifiable

ANY OTHER COMMENT: _____

NAME OF PERSON REPORTING: _____ DATE: _____

E-MAIL ADDRESS: _____ PHONE NO.: _____

DESIGNATION: _____ SIGNATURE: _____

You need not be certain ... just be suspicious !

You support to this Pharmacovigilance program is appreciated.

Submission of a complaint does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the regional pool of drug safety and therapy in Kenya. Once completed please send to:
The Pharmacy and Poisons Board at the above address

EXPLANATORY NOTES

CONFIDENTIALITY
All information collected in this form, identities of the reporter and patient, will remain confidential

WHAT HAPPENS TO THE SUBMITTED INFORMATION
All information submitted is handled in strict confidence. The Pharmacy and Poisons Board will assess causality and statistical analysis on each form. Data will periodically be used for review and support any interventions that may be required by the Ministry of Health. Data will also be submitted periodically to the Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring in Sweden.

WHAT TO REPORT
An Adverse Drug Reaction (ADR) is defined as a reaction that is noxious and unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or treatment of a disease, or for modification of physiological function.

Report all suspected adverse experiences with medications, especially those where the patient outcome is:
- Death
- Life-threatening (need risk of dying)
- Hospitalization (initial or prolonged)
- Disability (significant, persistent or permanent)
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:
- You are not certain if the drug caused the reaction
- You do not have all the details

SUBMISSION OF INITIAL OR FOLLOW-UP REPORTS
It is important to tick the appropriate box on the top-right corner of the front page to indicate whether the report is an initial (original) report or is a follow-up (subsequent) report.
It is very important that follow-up reports are identified and linked to the original report.

WHERE TO REPORT
After completing this form, please forward the same to your Pharmacy Department for onward submission, or mail directly, to:

THE PHARMACY AND POISONS BOARD
Lenana Road,
P. O. Box 27663-00506 NAIROBI
Tel: (020)-2716905 / 6 Ext 114 Fax: (020)-2713431/2713409
E-mail: pv@pharmacyboardkenya.org

WHO CAN REPORT
All healthcare professionals (clinicians, dentists, nurses, pharmacists, physiotherapists, community health workers etc) are encouraged to report. Patients (or their next of kin) may also report.

Please use the space provided below for any further information. You may attach more pages to this form if required.

LIST OF ALL DRUGS USED IN THE LAST 3 MONTHS PRIOR TO REACTION (include OTC and herbals)	DOSE	ROUTE AND FREQUENCY	DATE STARTED	DATE STOPPED	INDICATION	TICK (√) SUSPECTED DRUG(S)
6						
7						
8						
9						
10						

Criteria for Assessment of Severity of an ADR

Mild	• The ADR requires no change in treatment with the suspected drug • The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required • No increase in length of stay
Moderate	• The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. • Increases length of stay by at least one day • The ADR is the reason for admission
Severe	• The ADR requires intensive medical care • The ADR causes permanent harm to the patient
Fatal	• The ADR either directly or indirectly leads to the death of the patient

WHO-UMC Causality Assessment Scale

Causality Term	Assessment
Certain	• Event of laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically *(i.e an objective and specific medical disorder or a recognized pharmacological phenomenon)* • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be explained by disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drugs / withdrawal lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drug provides plausible explanation
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper, assessment needed or • Additional data under examination
Unassessable/ unclassifiable	• Report suggesting an adverse reaction • No information to the contrary or contradictory information • Data cannot be supplemented or verified

Your support to this Pharmacovigilance program is appreciated.

Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the event.
Patient's identity is held in strict confidence and programme staff is not expected to and will not disclose reporter's identity in response to any public request.
Information supplied by you will contribute to the regional pool of drug safety and therapy in Kenya.
Once completed please send to: The Pharmacy and Poisons Board on the above address

Appendix III: Adverse reactions associated with antibiotics (79,80)

Antibiotic Class	Examples	Potential adverse reactions
Penicillins	penicillin, amoxicillin	rash, diarrhea, abdominal pain, nausea/vomiting, drug fever, hypersensitivity (allergic) reactions
Cephalosporins	cephalexin, cefuroxime, ceftriaxone	hypersensitivity (allergic) reactions, serum sickness, vaginal candidiasis
Aminoglycosides	gentamicin, streptomycin	renal toxicity, ototoxicity
Carbapenems	meropenem, imipenem-cilastatin	diarrhea, nausea/vomiting, headache, rash, liver toxicity, eosinophilia (elevated white blood cells)
Antituberculosis agents	rifampin, rifabutin, isoniazid, pyrazinamide, ethambutol,	hemolytic anemia, liver toxicity, peripheral neuropathy, reddish-orange body fluids (rifampin, rifabutin)
Glycopeptides	vancomycin, televancin	red man syndrome (flushing, hypotension, itching); phlebitis nephrotoxicity taste alteration, nausea/vomiting, headache, dizziness
Macrolides	erythromycin, azithromycin, clarithromycin	QT prolongation Gastrointestinal distress, taste alterations
Sulfonamides	trimethoprim-sulfamethoxazole, sulfadiazine	hypersensitivity, photosensitivity, hematological effects
Tetracyclines	tetracycline, doxycycline	tooth discoloration in children < 8 years, liver toxicity photosensitivity
Quinolones	ciprofloxacin, levofloxacin	Photosensitivity, QT prolongation Dysglycemia
Lincosamide	clindamycin, lincomycin	pseudomembranous colitis, hypersensitivity, jaundice
Nitroimidazoles	metronidazole	metallic taste, peripheral neuropathy

Appendix IV: Type and organ system affected by reported adverse drug reaction (n=637)

Adverse drug reaction by organ system	n (%)
Integumentary	
Skin rash	253 (39.7)
SJS	39 (6.1)
Pruritus	37 (5.8)
Skin hyperpigmentation	29 (4.6)
Skin desquamation	10 (1.6)
TEN	6 (0.9)
Skin hypopigmentation	3 (0.5)
Burning sensation on skin	2 (0.3)
Itch at site of injection	2 (0.3)
Skin flushing	2 (0.3)
Erythrema multiforme	1 (0.2)
CNS/PNS	
Peripheral neuropathy	25 (3.9)
Dizziness	13 (2.0)
Ototoxicity	12 (1.9)
Headache	6 (0.9)
Convulsions	5 (0.8)
Confusion	2 (0.3)
Eye inflammation	2 (0.3)
Headache	2 (0.3)
Ocular toxicity	2 (0.3)
Ataxia	1 (0.2)
Loss of consciousness	1 (0.2)
Psychosis	1 (0.2)
GIT	
Oral ulcers	37(5.8)
Vomiting	11 (1.7)
Abdominal pain	8 (1.3)
Diarrhoea	4 (0.6)
Dysphagia	4 (0.6)
Nausea	4 (0.6)

Adverse drug reaction by organ system	n (%)
Swelling of lips	4 (0.6)
Burning sensation on lips	2 (0.3)
Loss of taste	1 (0.2)
Endocrine	
Hepatotoxicity	35 (5.5)
Nephrotoxicity	5 (0.8)
Hyperthyroidism	1 (0.2)
Others	
Malaise	6 (0.9)
Red coloured urine	6 (0.9)
Shivering	5 (0.8)
Collapsed and died	2 (0.3)
Night sweats	1 (0.2)
Respiratory	
Respiratory distress	10 (1.6)
Cough	1 (0.2)
Cardiovascular system	
Anaemia	5 (0.8)
Palpitations	4 (0.6)
Musculoskeletal	
Arthralgia	7 (1.1)
Back pain	1 (0.2)
Reproductive	
Genital blisters	2 (0.3)
Loss of libido	1 (0.2)

SJS-Steven-Johnson syndrome, TEN- toxic epidermal necrolysis

Appendix V: Suspected drug and antibiotic class causing reported adverse drug reactions from the PPB database

ANTIBIOTIC CLASS	SUSPECTED DRUG	n (%)
Sulphonamides	Cotrimoxazole	304 (55.3)
	Total	304 (55.3)
Anti-tuberculosis	Isoniazid	43 (7.8)
	RHZE	16 (2.9)
	Rifampicin	12 (2.2)
	RHZ	9 (1.6)
	Cycloserine	4 (0.7)
	Pyrazinamide	3 (0.5)
	Ethambutol	1 (0.2)
	RHE	1 (0.2)
	Total	89 (16.2)
Penicillins	Amoxicillin	11 (2.0)
	Benzyl penicillin	11 (2.0)
	Amoxicillin/clavulanic acid	9 (1.6)
	Ampicillin/cloxacillin	5 (0.9)
	Benzathine penicillin	2 (0.4)
	Ampicillin	2 (0.4)
	Flucloxacillin	1 (0.2)
	Fortified procaine penicillin	1 (0.2)
	piperacillin/tazobactam	1 (0.2)
	Total	43 (7.8)
Aminoglycosides	Kanamycin	12 (2.2)
	Streptomycin	11 (2.0)
	Amikacin	1 (0.2)
	Gentamycin	1 (0.2)
	Streptomycin/penicillin	1 (0.2)
	Total	26 (4.7)
Quinolones	Ciprofloxacin	15 (2.7)
	Levofloxacin	6 (1.1)
	Moxifloxacin	1 (0.2)
	Norfloxacin	1 (0.2)
	Total	23 (4.2)
Cephalosporins	Ceftriaxone	10 (1.8)
	Cefuroxime	4 (0.7)
	Cephalexin	2 (0.4)
	Cefadroxil	2 (0.4)

ANTIBIOTIC CLASS	SUSPECTED DRUG	n (%)
	Total	18 (3.3)
Nitroimidazoles	Metronidazole	6 (1.1)
	Tinidazole	4 (0.7)
	Secnidazole	2 (0.4)
	Total	12 (2.2)
Antifungals	Amphotericin B	5 (0.9)
	Griseofulvin	3 (0.5)
	Fluconazole	1 (0.2)
	Total	9 (1.6)
Lincosamides	Clindamycin	7 (1.3)
	Lincomycin	1 (0.2)
	Total	8 (1.5)
Macrolides	Azithromycin	4 (0.5)
	Clarithromycin	2 (0.4)
	Erythromycin	2 (0.4)
	Total	8 (1.5)
Glycopeptides	Vancomycin	4 (0.7)
	Total	4 (0.7)
Others	Nitrofurantoin	2 (0.4)
	Bacitracin	1 (0.2)
	Chloramphenicol	1 (0.2)
	Total	4 (0.7)
Tetracyclines	Doxycycline	2 (0.4)
	Total	2 (0.4)
Grand Total		550

RHZE – rifampicin/isoniazid/pyrazinamide/ethambutol, RHZ – rifampicin/isoniazid/pyrazinamide, RHE – rifampicin/isoniazid/ethambutol

Appendix VI: Adverse drug reactions due to sulphonamides (n=304)

Adverse drug reaction by organ system	n (%)
Integumentary	
Skin rash	163 (53.6)
SJS	33 (10.9)
Skin hyperpigmentation	22 (7.2)
Pruritus	19 (6.3)
Skin desquamation	7 (2.3)
Skin hypopigmentation	3 (1.0)
TEN	3 (1.0)
Burning sensation on skin	2 (0.7)
GIT	
Oral ulcers	21 (6.9)
Burning sensation on lips	4 (1.3)
Epigastric pain	3 (1.0)
Swelling of lips	2 (0.7)
CNS/PNS	
Eye inflammation	2 (0.7)
Headache	1 (0.3)
Paraesthesia	1 (0.3)
Convulsions	1 (0.3)
Cardiovascular	
Anaemia	4 (1.3)
Endocrine	
Hepatotoxicity	2 (0.7)
Nephrotoxicity	1 (0.3)
Reproductive	
Genital blisters	2 (0.7)
Respiratory	
Respiratory distress	2(0.7)
Others	
Malaise	1 (0.3)
Not specified	5 (1.6)

Appendix VII: Adverse drug reactions due to anti-tuberculosis agents

Adverse drug reaction by organ system	n (%)
CNS/PNS	
Peripheral neuropathy	21 (18.9)
Dizziness	5 (4.5)
Headache	2 (1.8)
Loss of eye sight	1 (0.9)
Psychosis	1 (0.9)
Endocrine	
Hepatotoxicity	30 (27.0)
Integumentary	
Skin rash	12 (10.8)
Pruritus	1 (0.9)
SJS	1 (0.9)
GIT	
Oral ulcers	4 (3.6)
Abdominal pain	3 (2.7)
Vomiting	3 (2.7)
Nausea	3 (2.7)
Others	
Malaise	6 (5.4)
Red coloured urine	6 (5.4)
Musculoskeletal	
Athralgia	6 (5.4)
Reproductive	
Loss of libido	1 (0.9)
Cardiovasular system	
Palpitations	1 (0.9)

SJS – Steven-Johnson syndrome

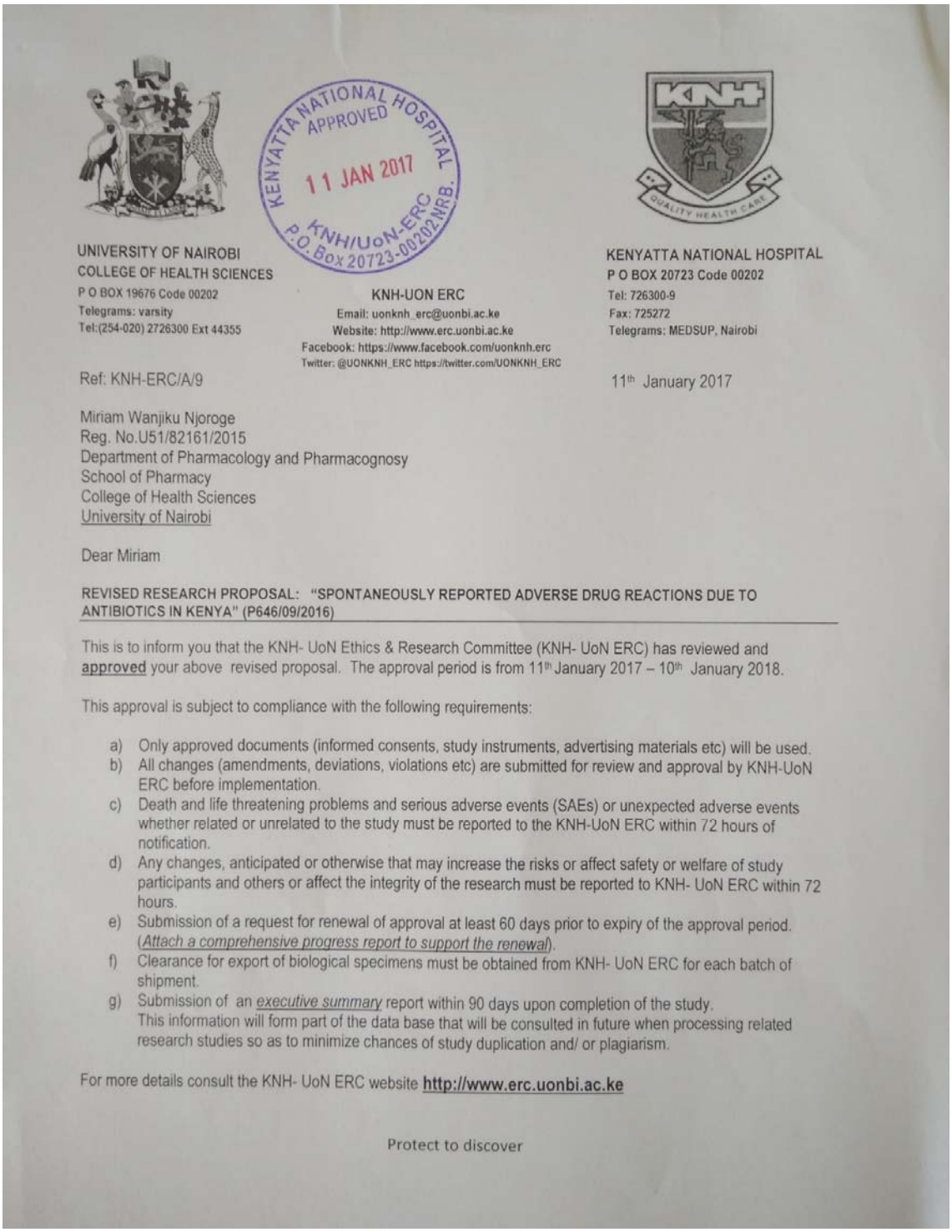
Appendix VIII: The concomitant drugs used by study subjects (n=403)

Medication	n (%)
ARVs	**141 (35)**
TDF/3TC/EFV	62 (15.4)
AZT/3TC/NVP	47 (11.7)
AZT/3TC/EFV	13 (3.3)
AZT/3TC/LOP/r	4 (1.0)
ABC/3TC/NVP	3 (0.7)
D4T/3TC/NVP	3 (0.7)
D4T/3TC/EFV	2 (0.5)
TDF/3TC/LOP/r	2 (0.5)
ABC/3TC/EFV	2 (0.5)
ABC/3TC/LOP/r	1 (0.2)
AZT/ABC/LOP/r	1 (0.2)
TDF/3TC/FTC	1 (0.2)
Pain relievers	**93 (23.1)**
Paracetamol	57 (14.1)
Ibuprofen	15 (3.7)
Diclofenac	12 (3.0)
Tramadol	6 (1.5)
Pethidine	2 (0.5)
Baclofen	1 (0.2)
Micronutrients	**74 (18.4)**
Multivitamin	38 (9.4)
Pyridoxine	30 (7.4)
Folic acid	3 (0.7)
Neurobione	2 (0.5)
Vitamin C	1 (0.2)
GIT-acting drugs	**22 (5.5)**
Omeprazole	9 (2.2)
Albendazole	5 (1.2)
Esomeprazole	5 (1.2)
Hyoscine	1 (0.2)
Lansoprazole	1 (0.2)
Pantoprazole	1 (0.2)
Antihypertensives	**22 (5.5)**
Nifedipine	5 (1.2)
Acetyl salicylic acid	4 (1.0)

Medication	n (%)
Frusemide	4 (1.0)
Hydrochlorothiazide	2 (0.5)
Amlodipine/ramipril	1 (0.2)
Atenolol	1 (0.2)
Aldactone	1 (0.2)
Digoxin	1 (0.2)
Enalapril	1 (0.2)
Captopril	1 (0.2)
Telmisartan	1 (0.2)
Antimalarials	**19 (4.7)**
AL	16 (4.0)
Quinine	3 (0.7)
Others	**12 (3)**
Acyclovir	3 (0.7)
Phenobabitone	3 (0.7)
Artovastatin	2 (0.5)
Combined oral contraceptives	2 (0.5)
Enoxaparin	1 (0.2)
Chlorpromazine	1 (0.2)
Antihistamines	**11 (2.7)**
Chlorpheniramine	10 (2.5)
Desloratidine	1 (0.2)
Antidiabetics	**9 (2.2)**
Metformin	4 (1.0)
Glibenclamide	3 (0.7)
Insulin	2 (0.5)
Total	**403**

3TC-lamivudine, ABC-abacavir, AZT-zidovudine, D4T-stavudine, EFV-efavirenz, FTC-emtricitabine, NVP-nevirapine, Lop/r-lopinavir/ritonavir, AL-artemether/lumefantrine

Appendix IX: KNH-UON Ethics approval



UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KENYATTA NATIONAL HOSPITAL APPROVED 11 JAN 2017 KNH/UoN-ERC P.O.Box 20723-00202 NRB.

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/9

11th January 2017

Miriam Wanjiku Njoroge
Reg. No.U51/82161/2015
Department of Pharmacology and Pharmacognosy
School of Pharmacy
College of Health Sciences
University of Nairobi

Dear Miriam

REVISED RESEARCH PROPOSAL: "SPONTANEOUSLY REPORTED ADVERSE DRUG REACTIONS DUE TO ANTIBIOTICS IN KENYA" (P646/09/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above revised proposal. The approval period is from 11th January 2017 – 10th January 2018.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

Protect to discover

Yours sincerely,

PROF M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Assistant Director, Health Information, KNH
The Chair, KNH- UoN ERC
The Dean, School of Pharmacy, UoN
The Chair, Dept.of Pharmacology and Pharmacognosy, UoN
Supervisors: Dr. Margaret Oluka, Dr.George Osanjo, Dr. Mercy Mulaku

Appendix X: Student confidentiality agreement form

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD

Telegram: "MINHEALTH" Nairobi
Telephone: 020-2716905/6, 020-3562107
Cellphone: 0733-884411/0720 608811
Fax: 2713409
Email: admin@pharmacyboardkenya.org
Website: www.pharmacyboardkenya.org

LENANA ROAD
P.O. BOX 27663-00506
NAIROBI

When replying please quote:
PPB/DBS/HR/GEN/Vol. I/17/003

6th April 2017

Miriam Wanjiku Njoroge,
Dept. of Pharmacology and Pharmacognosy
School of Pharmacy
University of Nairobi
Reg. No.:U51/82161/2015
NAIROBI

Dear Madam,

RE: Research thesis in Mpharm. Pharmacoepidemiology and Pharmacovigilance

Reference is made to your letter received at PPB on 4th April 2017, requesting for data collection on ***"Spontaneously reported adverse drug reactions due to antibiotics in Kenya."***

The Board allows you to go on with the study on conditions of the stipulated student confidentiality agreement enclosed herein.

Be informed that Pharmacy & Poisons Board shall terminate your study should any of the stated conditions be violated. Kindly note that the Board would like to be involved in the joint publication of your research findings.

You are further required to provide a copy of your final project work for information and future reference to the Medicines Information and Pharmacovigilance Directorate.

Yours faithfully,

Dr. F. M. Siyoi
For: REGISTRAR

CK/em

I confirm that I have no situation of real, potential or apparent conflict of interest including financial or other interests in, and/or other relationship with, a party, which:

(i) May have a vested commercial interest in obtaining access to any part of the Information referred to above; and/or

(ii) May have a vested interest in the outcome of evaluation of the application.

I shall promptly notify the Registrar, PPB of any change in the above circumstances, including if an issue arises during the course of my work.

All documents supplied to me in connection with this application shall be accepted in strict confidence and shall be held in safe and secure custody at all times.

I hereby accept and agree with the conditions and

Declaration:

I, the undersigned, do hereby agree to adhere to the provisions contained in this agreement.

I hereby declare that I ~~have/~~ do not have (*delete what is NOT applicable*) a Conflict of Interest with ~~the following application(s)~~/any of the applications that I have been requested to review (*delete what is NOT applicable*)

Reference number (s) of application (s) with which I have a conflict of interest

MIRIAM WANJIKU NJOROGE
(Student Name)

MNjoroge
(Signature)

7.4.2017
(Date)