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ADVERSE DRUG REACTIONS IN WEST AFRICA

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ABSTRACT

Adverse drug reaction (ADR) reports of countries varies due to differences in the prevalence of diseases and hence the types of drugs used. ADRs are a major health and economic burden worldwide. National health authorities monitor the safety of medicines to protect consumers from the hazards of drugs. ADR databases are also maintained from where reports are regularly evaluated to detect signals of new ADRs and determine the increase of those already known.

A review of paediatric and general population studies conducted on ADRs from national ADR databases was carried out. The majority of studies identified were from countries in Europe and North America, and only one study on the general population was conducted from the Ethiopian ADR database in Africa. No paediatric study was identified in Africa. Skin reactions associated with antiretroviral drugs were the most frequent ADRs in the study conducted from the Ethiopian ADR database. Anti-infective agents, mostly vaccines, were mostly associated with the ADRs in children in Europe and Latin America, and drugs used for treating attention deficit hyperactivity disorders (ADHD) were implicated with the ADRs reported for children in North America.

The ADR databases of Ghana and Nigeria were analysed to evaluate the ADRs reported for children and adults. The fatalities reported and the associated drugs in the two databases were also evaluated.

The ADR reporting rates for children and the general population in Ghana and Nigeria were lower than the corresponding rates observed in the review.

The majority of the ADRs in Nigerian adults were reported for antiretroviral drugs, and most of those who died suffered Stevens Johnson syndrome with antimalarials as the suspect drugs.

ADRs reported for Nigerian children were mainly skin reactions associated with antibiotics. Most of the reported fatalities resulted from renal failure, linked with suspected contaminated teething mixtures.

Antimalarials and anthelmintics were mostly associated with the ADRs in Ghanaian adults. Most of the reported fatalities resulted from Stevens Johnson syndrome.

ADRs in Ghanaian children were mostly associated with vaccines. The majority of the reported deaths resulted from unknown causes linked with antimalarials.

DEDICATION

This work is dedicated to my dependants, especially Amifel Cliff-Eribo and Nanighe Idumesaro, who have endured the partial – fulfilment of my promise to support them during the course of this study. I thank them all for their patience and understanding.

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- 2. Cliff-Eribo KO**, Choonara I, Dodoo A, Darko D, Sammons H. Adverse Drug Reactions in Ghanaian Children - Review of reports from 2000 to 2012 in VigiBase. Expert Opin Drug Saf. 2015 Oct 5:1-7.

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LIST OF ABBREVIATIONS

ACT	Artemisinin Combination Therapy
ADE	Adverse Drug Event
ADHD	Attention Deficit Hyperactivity Disorder
ADRs	Adverse Drug Reactions
AIDS	Acquired Immune Deficiency Syndromes
ATC	Anatomic Therapeutic Class
DPA	Disproportionality Analysis
EEA	European Economic Area
EML	Essential Medicines List
EPI	Expanded Programme on Immunisation
EU	European Union
FDIC	Food and Drug Information Centre
Ghana FDA	Ghana Food and Drugs Authority
HCPs	Healthcare Professionals
HIV	Human Immunodeficiency Virus
IC	Information Component
ICH	International Conference on Harmonisation
IPTi	Intermittent Preventive Treatment in infants
MAHs	Marketing Authorisation Holders
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NAFDAC	National Agency for Food and Drug Administration and Control
NPCs	National Pharmacovigilance Centres
PEM	Prescription Event Monitoring

PEPFAR	President's Emergency Plan for AIDS Relief
PRRs	Proportional Reporting Ratios
PV	Pharmacovigilance
RORs	Reporting Odds Ratios
SJS	Stevens Johnson syndrome
SOC	System Organ Class
STGs	Standard Treatment Guidelines
TEN	Toxic Epidermal Necrolysis
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
USA	United States of America
US-FDA	United States Food and Drug Administration
WHO	World Health Organisation
WHO-ART	WHO Adverse Reaction Terminology
WHO-DD	WHO Drug Dictionary

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CHAPTER ONE

GENERAL INTRODUCTION

1.1 Adverse Drug Reactions

A drug was initially thought to act on one target with one causal effect. However, research on adverse effects of drugs in cells has shown that this is not always the case, as both beneficial and harmful effects can be produced [1], as demonstrated by the thalidomide disaster in the early 1960s [2]. Modern drugs are designed to regulate the functions of specific target proteins, or act directly on target organs to remedy failing functions of the body. In the process of trying to protect the organs from drugs which the body considers as foreign, potentially harmful effects are generated. Similarly, potential unwanted side effects are produced when drugs act on off-target proteins [3].

It is well known that all drugs carry the potential to produce both desirable and undesirable effects even if correctly selected and dosed [3]. However, certain unintended effects (i.e. side effects) – although normally undesirable, can also be beneficial for other disease conditions. For example, sildenafil was developed for angina but its side effects became useful for the treatment of erectile dysfunction and pulmonary hypertension [4].

A clear distinction exists between an adverse drug event (ADE) and adverse drug reaction (ADR). An ADE is any undesirable event experienced by a patient whilst taking a drug, regardless of whether the drug is suspected to be related to the event. For example, a patient having a road traffic accident while on a specific medication. Adverse drug events are therefore

undesirable events experienced when drugs are used (including overdose, dose reduction and discontinuation of therapy) [5]. If the effect is causally related to the drug, it is termed an ADR. Consequently, an ADR is defined by the World Health Organisation (WHO) as: (please see Box 1.1 for definition) [6].

Box 1. 1: Definition of ADR

“a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function”

An ADR is defined as serious if it is life threatening or caused/prolonged hospitalisation, disabling/incapacitating, congenital anomaly/birth defect or death [7]. There are many types of ADRs, and they are classified according to the nature of reaction experienced and system of the body affected.

1.2 Classification of adverse drug reactions

Adverse drug reactions are categorised as type A (pharmacological) or type B (idiosyncratic) [8].

Type A (Augmented) reactions represent an augmentation of the pharmacological actions of a drug. They are dose-dependent and are readily reversible when the dose of the drug is reduced or withdrawn. Type A reactions are predictable and are not generally severe.

In contrast, Type B (Bizarre) adverse reactions often cannot be predicted from the known pharmacology of the drug. They are not dose-related and may be severe or fatal. Many Type B reactions have an immunological basis. Genetic pre-disposition of the patient may be an important factor in these reactions.

Other forms of classification include Type C (chronic), Type D (delayed), Type E (end of treatment) and Type F (failure of treatment) [9].

Type C (Chronic) ADRs are dose and time related reactions and are associated with long-term use and involve dose accumulation. For example, hypothalamic pituitary adrenal axis suppression by corticosteroids [10], interstitial nephritis from the long-term usage of phenacetin [11], and ocular toxicity by antimalarials [12].

Type D (Delayed) ADRs are associated with delayed reactions which sometimes occur after the use of the drug, such as in teratogenesis (e.g., fetal hydantoin syndrome) or in long term treatment of cancer (e.g. late secondary cancers seen after chemotherapy treatment of leukaemia).

Type E (End of treatment) ADRs are associated with withdrawal reactions, and these occur at the end-of-treatment, i.e., where discontinuation is too abrupt, for example, rebound adrenocortical insufficiency, pulmonary oedema after stopping diuretics or opiate withdrawal syndrome.

Type F (Failure of treatment) ADRs occur in unexpected failure of therapy i.e., as in failure of treatment, often caused by drug interaction or inadequate drug dosage.

The WHO has also classified adverse drug reactions according to the organs of the body affected, called 'system organ class', and this system is used worldwide for the coding of ADRs in pharmacovigilance practice [13].

1.3 Epidemiology

Adverse drug reactions are among the top ten leading causes of death and illness in the world, and they ranked between fourth and sixth as a major cause of death in USA [14]. Studies have also shown that patients experiencing ADRs have a two-fold increased risk of death [15]. The prevalence of reported ADRs in patients in hospital in some countries is more than ten percent. It is 11.5% in Norway [16], 13% in France [17], 16% in the UK [18] and between 10–30% in a number of developing countries including Nigeria [19].

The incidence of definite and probable ADRs in hospitalised children in UK has been estimated as 15.9% [20]. In this prospective observational study, 58% of the ADRs occurred in children undergoing procedures under general anesthesia. The most common reactions observed were nausea and/or vomiting, pruritus and constipation. However, in a previous prospective observational study of acutely hospitalised children, the incidence of ADRs was estimated at 2.9 per 100 admissions. 48.2% of the ADRs resulted from treatment for malignancies. The drugs implicated were mainly cytotoxic agents and corticosteroids, and the most common ADRs were neutropenia, immunosuppression and thrombocytopenia [21].

In a meta-analysis of 17 prospective studies conducted in USA and Europe [14], incidence of ADRs in children has been estimated as 9.5%, of which

12% were serious reactions. The study estimated the overall rate of paediatric hospital admissions due to ADRs as 2.09%, of which 39.3% were life-threatening, and the overall incidence of ADRs for outpatient children as 1.46%. In another review of observational studies in children, incidence rates of ADRs causing hospital admission ranged from 0.4% to 10.3%, and the incidence rates for children exposed to a drug during hospital stay ranged from 0.6% to 16.8% [22]. This underscores the need to ensure drugs prescribed to children are safe.

A qualitative review of studies monitoring ADRs in children showed higher numbers of ADRs were reported in national ADR databases than in studies monitoring hospital patients [23]. This was attributed to the longer period of data collection in national ADR databases and the larger populations covered.

1.4 Economic implications of adverse drug reactions

There is a huge financial burden and human suffering associated with ADRs. In a prospective analysis of ADRs experienced by patients (aged 16 years and above) in two hospitals in UK over a 6-month period, Pirmohamed and colleagues [24] reported 6.5% of admissions were related to ADRs, and among these, 80% were judged to be directly responsible for admissions with an overall fatality rate of 0.15%. The median bed stay in this study was eight days. This made up 4% of the hospital bed capacity with a projected annual cost of £466m to the National Health Service. In another study on the economic impact of ADR-related hospital admissions and readmissions, Dormann and colleagues [25] reported that ADRs resulted in hospitalisation

of 6.2% of first time admissions and 4.2% of readmitted patients within an 18-month study period. ADR-related costs in this study were estimated to be more than 350,000 Euros in 12 months.

ADRs have also been reported to impose a high financial burden on patients in Nigeria [26], and some countries have earmarked between 15 – 20% of national budgets for the treatment of drug related diseases [27]. It is important to stress that drugs are a major contributor to any successful healthcare programme. Therefore, the availability of adequate information on ADRs in the population is an important consideration for planning in any national healthcare system.

1.5 Adverse drug reactions in children

The safety of medicines in the paediatric population is a key issue that requires more in-depth study [28], because some disease processes and their treatment are more common in childhood than in adulthood. In addition, the identification and reporting of ADRs in children is difficult for several reasons:

- Children have different pharmacokinetics and dynamics compared to adults [29], and therefore have particular vulnerability to ADRs. For example, a premature infant has less fat by body weight to distribute fat soluble drugs than full-term infants or older children. Therefore, the levels of lipophilic drugs in the blood might be significantly higher in this age group.
- Children are growing and may be susceptible to developmental disorders, as well as delayed ADRs not seen in adults. For example, if

tetracycline is given to infants and young children during the period when their teeth are being formed (up to age 8 years), it may permanently discolour tooth enamel.

- In addition, certain ADRs may only be seen in children, for example; children under the age of 18 years are at risk of Reye's syndrome if they are given aspirin while they have a viral infection [30].
- Efficacy of drugs in children cannot always be assumed from adult efficacy data, for example, children who received dihydroartemisinin-piperaquine for uncomplicated *Falciparum* malaria had a higher cure rate compared to adults [31].
- Most children, especially in the early stage of life, are not able to take solid drug formulations; therefore drugs are often prepared in liquid forms. These liquid forms contain excipients to improve drug stability. However, excipients have an independent risk of ADRs and may also generate adverse effects in children. For example, an excess amount of alcohol in phenobarbital solution formulations can increase possible unpleasant effects in children [32].
- Many medicines are used in paediatrics in an off-label or unlicensed manner due to lack of clinical trials in children, and consequently product information to support safe use in children are inadequate. A study conducted by Impicciatore and colleagues found that 38% of ADRs which occurred in inpatients, and 42% of ADRs that led to hospitalisation were related to off-label drugs [33].
- Inability of many children to evaluate and state their own reaction to medications and explain adverse effects that they might experience.

This is an important issue that make ADRs more difficult to detect and increase their risk in children [30].

Due to developmental changes taking place during the years of growth, ADRs in children can have different effects, which can lead to significant morbidity when compared to adults [23]. Data on the frequency, severity and types of drugs most frequently associated with adverse reactions in children are generally not available [34], since pre-marketing clinical trials are mostly based on adults [35].

It has been observed that ADRs in children not only result in hospital admissions or prolonged hospitalisation but may also lead to permanent disability or even death [36]. However, in two separate prospective observational studies conducted in UK, many ADRs in hospitalised children were either definitely or possibly avoidable [20, 21].

The safety profile of a marketed drug that is tested only on adults can vary significantly when used in children [35]. Therefore, it is important to involve children in clinical trials when possible, in addition to continuous monitoring and reporting of ADRs experienced to obtain safety data [37].

1.6 Pharmacovigilance

Pharmacovigilance (PV) has been defined by WHO as: (please see Box 1.2 for definition) [38].

Box 1. 2: Definition of Pharmacovigilance

“the science and the group of activities related to detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem”

It is a key public health function and represents a complex network of activities that involves the surveillance of undesirable effects of drugs with the primary aims of providing updated information about drug safety and of defining the risk/benefit ratio for the drugs [39]. In short, PV is the process of monitoring medicines to bring about their safe use by the public. It involves detection of signals of new or potentially unknown adverse reactions associated with drugs in an ADR database, and taking necessary action to protect users of such drugs from further harm. Pharmacovigilance activities are therefore aimed at providing protection to the public from the harm caused by medicines while also promoting their benefits [38].

Modern pharmacovigilance came into being after the Thalidomide disaster in the 1960s [2], when children were born with limb deformities by women who took thalidomide in early pregnancy. As response to this disaster, The WHO Research Centre for International Monitoring of Adverse Reactions to Drugs was established in 1978 to monitor ADRs worldwide, and since then, health

authorities in several countries have put in place pharmacovigilance processes to perform these functions.

The WHO Centre is responsible for developing methodologies to support global pharmacovigilance systems [40]. Indeed, pharmacovigilance has become an integral part of healthcare delivery among many nations and in pharmaceutical manufacturing. However, whereas ADR reporting activities are well developed in Western countries, the situation is in its infancy in many developing countries, including those in West Africa [19].

ADRs experienced in countries around the world vary in frequency and incidence due to differences in the types of drugs used, age, sex and genetic make-up of the populations, as well as social, economic and environmental factors [41]. Pharmacovigilance practice is also incorporated in the National Health Systems in Ghana and Nigeria, and both countries maintain ADR databases. The PV databases of many countries have been described to characterise and document ADRs that have been reported for drugs being used in the population. This has not been carried out in Ghana and Nigeria. Characterisation and documentation of reported ADRs in databases can help with public health planning and healthcare delivery in these countries.

1.7 Adverse drug reaction reporting

Clinical trials are not usually powered to detect toxicity. However, in trials which enrol 3000 or more participants, at least one uncommon event may be observed [42], and the incidence of some rare side-effects is below one in 10,000 reports [43]. Consequently, rare/uncommon ADRs are unlikely to be

reported in randomised clinical trials, and hence there is need for continued assessment of drugs approved for public use. In Europe, Market Authorisation Holders (MAHs) of drugs are legally required through the New European Union Pharmacovigilance Regulation to monitor their products in countries where they are marketed [44]. This requirement also applies to drugs that are to be used in population groups excluded in the corresponding clinical trials. It is also a legal requirement for pharmaceutical companies to send spontaneous reports of ADRs to health authorities of countries where their products are marketed. The health authorities maintain databases which contain these reports, and these are used to assess the continued safety of the products.

Various pharmacovigilance schemes exist in different healthcare systems. In United Kingdom, the Medicines and Healthcare products Regulatory Agency (MHRA) request anyone, including doctors, dentists, nurses, pharmacists, coroners and patients/consumers to report suspected ADRs via the Yellow Card Scheme [45]. A Yellow Card is used to collect information about the patient, suspected drug(s), suspected reaction(s) and reporter details and is then sent to MHRA.

The MHRA has recently updated the Yellow Card Scheme to harmonise the guidelines for reporting paediatric and adult ADRs [46]. In this update, all suspected ADRs associated with new drugs and vaccines and those that require additional post-marketing surveillance in Europe, which are identified by an inverted black triangle (▼), are reported to MHRA. In addition, all suspected serious ADRs (defined as those that are life-threatening, incapacitating, or resulted in permanent disability, hospitalisation or death,

and others considered medically significant) are reported. Mandatory reports from pharmaceutical companies on adverse events that had been spontaneously communicated to the firms primarily by healthcare professionals are also received by MHRA. In addition to the Yellow Card Scheme, the Prescription Event Monitoring (PEM) scheme monitors the overall safety of newly marketed medicines used in real-life clinical practice [47]. It does so by identifying all patients prescribed the drug through an electronic system, and collating all details of ensuing new events subsequently submitted by their general practitioners.

The Yellow Card System is also adopted by Sweden, Norway and Nigeria, and the Blue Card System operates in Australia [19, 48]. Other countries, including Ghana, have similar systems for the collection of ADR data from healthcare professionals and consumers. In the United States, the Food and Drug Administration (FDA) directly receives voluntary ADR reports from the public and healthcare professionals, and mandatorily from pharmaceutical manufacturers via the MedWatch programme [49].

For the effective collection of ADR reports, regional pharmacovigilance centres have been established in some countries, such as Sweden and France [47], Cuba [50], Korea [51] and India [52], where reports of ADRs are received from notifiers and forwarded to the national centres.

At the international level, the Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre – UMC), manages a database (VigiBase) of ADR reports received from registered National Pharmacovigilance Centres throughout the world [53]. The International

Centre also standardises ADR reporting for all the registered National Centres and facilitates communication between participating countries to promote rapid identification of signals [54].

1.8 Causality assessment

It is not straight forward to determine whether an event is an ADR. The process involves combination of experience on the part of the reporter/and or ADR assessors. In most cases, clinicians assume knowledge of the pharmacological properties of the drug to determine if a reaction is caused by the drug which is considered as suspect at the time of reporting [9].

For an individual case safety report to be valid, it must include a reporter, patient identifier, an ADR, and a suspect drug. Routine causality assessment is usually part of the first step in case assessment and success depends on the completeness of the individual case safety reports. All information about the patient's medical condition and the suspect drug(s) including dosage are reported. The outcome of the ADR when the drug was de-challenged and re-challenged is also reported. In addition to the suspect drug, concomitant medications taken by the patient over the period of time ADR was experienced are also reported. However, most individual case safety reports do not contain all the required information needed for causality assessment of the drugs [55].

In Ghana and Nigeria, causality assessments of drugs are usually carried out at regular intervals by a team of experts which involve clinical pharmacologists, pharmacists and pharmacovigilance professionals [19, 56].

The team is also called upon when an urgent need arises for an assessment [19].

Various causality assessment procedures have been described [57]. However, the WHO – UMC has set out criteria for assessing causality, and this is based on combined assessment taking into account the clinico-pharmacological aspects of the case history and quality of documentation of the report. The causality terms used are certain, probably/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable (please see Box 1.3 for definition of causality terms) [9]. Complete documented reports in ADR databases in addition to assessment of causality for the drugs enhance signal detection of most unknown drug reactions.

Box 1. 3: Definition of causality terms

“Certain

- *A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals*
- *The response to withdrawal of the drug (dechallenge) should be clinically plausible*
- *The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary*

“Probably/likely

- *A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge)*
- *Rechallenge information is not required to fulfil this definition*

“Possible

- *A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals*
- *Information on drug withdrawal may be lacking or unclear*

“Unlikely

- *A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations*

“Conditional/unclassified

- *A clinical event, including a laboratory test abnormality, reported as an adverse reaction, but which more data are essential for a proper assessment or the additional data are being examined*

“Unassessable/unclassified

- *A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified”*

1.9 Signal detection

Reports in health authority databases are periodically analysed to determine if there are signals that need further investigation to protect the public from potential harm caused by drugs. Spontaneous ADR data collected over a period of time therefore serve as an effective resource for the early detection of new ADRs and of those previously unknown [58], as well as for determining possible aetiologies and risk factors for certain ADRs [59]. The WHO has therefore defined a drug safety signal as: (please see Box 1.4 for definition) [60].

Box 1.4 Definition of safety signal

“reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”

To ensure the public is protected, data mining have been employed to facilitate the identification of either new safety issues or possible harmful effects of a product. Data mining or disproportionality analysis (DPA) is a technique for extracting meaningful, organised information from large complex databases [61]. It involves identification of drugs and adverse events that are reported more frequently than expected by using information on all drugs and all events in the database to estimate expected reporting frequencies.

Various methods of detecting signals in ADR databases have been described, and the effectiveness of these processes largely depends on size of the data. The Proportional Reporting Ratios (PRRs) method is used by the MHRA in United Kingdom [62]. The pharmacovigilance centre in The Netherlands uses the Reporting Odds Ratios (RORs) method [63], whereas the UMC in Sweden uses the Information Component (IC) method to monitor signals [64]. The RORs and IC are complex data mining tools which have the possibility of sorting many drug-event combinations. They are also less susceptible to the effect of small random fluctuations, and involve the use of logistic regression which facilitates adjusting for confounding factors such as other drugs, age or gender [65]. However, the complexity of the mathematical

models involved in both methods is generally considered as their main disadvantage as well as the fact that they are not necessarily superior to the PRRs approach [66]. The PRRs are simple to calculate and interpret. However, by determination, very strong signals for a particular drug may as a result reduce the PRRs of other signals of the same drug, and this effect is attributed to the inflation of the denominator of the drug by large numbers of reports of a particular kind [67].

1.10 Regulatory decisions

Spontaneous reporting in pharmacovigilance is a process of data acquisition, assessment, presentation and interpretation. Definitive outcomes are not always arrived at when signal detection procedures are performed in an ADR database, and regulatory decision cannot be taken based on a single signal detected for a particular drug. The signals detected are therefore considered as hypotheses and are further investigated to determine if they are indicative of safety concerns [68]. The health authorities utilise the outcome of these investigations to confirm authenticity of signals before making regulatory decisions on further use of identified drugs.

1.11 Aim of this thesis

ADRs can impact on the health of people and economic well-being of a nation. ADR reports in national databases represent the ADR status of the population of the country and regulatory authorities utilise ADR information in these databases to make decisions on drug products suspected to be harmful to consumers.

This research is aimed at describing the ADR reports in Ghana and Nigeria. Ghana and Nigeria were chosen for the research in view of the similarities in their healthcare delivery system. Both countries speak English and are located in the tropics with similar culture. There is a high prevalence of HIV/AIDS in Nigeria and worm infestation in Ghana. Malaria is endemic in both countries.

The two countries operate a 3-tier system of healthcare delivery – primary, secondary and tertiary healthcare. The primary healthcare service is provided in health centres by the local councils. The regional and state governments provide secondary healthcare services in the general or regional hospitals, and the tertiary services are provided in university teaching and specialist hospitals by the federal governments. In addition to these services, patients receive medical care from private healthcare providers and traditional healers. The ministry of health in the two countries regulates the healthcare delivery system. Both countries have national pharmacovigilance centres, and submit ADR reports to the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, that are yet to be analysed.

Also in this thesis, a literature review of descriptive studies of ADRs conducted on national ADR databases will precede the ADR analyses from Ghana and Nigeria. The most commonly reported ADRs and drugs will be determined, and differences between countries in relation to success in the reporting of ADRs will be evaluated.

In the databases of the two countries, the ADR reports will separately be analysed for children aged 0 – 17 years, and adults aged 18 years and above

to: (1) determine the number of reports received per year, (2) identify notifiers of ADRs, (3) identify types of ADRs and drugs reported, (4) evaluate causality assessment of drugs, and (5) identify reports of death and drugs implicated. A comparison of the general reports between both countries will also be made.

It is hoped that the thesis will stimulate interest in pharmacovigilance in Africa. It is also hoped that the data collected and analysed will contribute to reducing drug toxicity in both children and adults in Africa.

CHAPTER TWO

LITERATURE REVIEW – DESCRIPTIVE ANALYSIS OF ADRs FROM NATIONAL PHARMACOVIGILANCE DATABASES

2.1 BACKGROUND

Adverse drug reactions vary significantly in type and frequency between countries. This is influenced by the incidence and prevalence of diseases, the country's economy, and physician's prescribing patterns and awareness to report ADRs on the part of healthcare professionals (HCPs) [69, 70]. The cumulative reports in databases help to detect rare/unexpected and serious ADRs not experienced during pre-marketing clinical trials [71], and serve as a means of developing pharmacovigilance methodologies to minimise risks with medicines and improve patient safety.

Databases are useful resources for healthcare research [72]. However, their usefulness in drug safety studies can be enhanced by improvement in their organisation, data quality, and usage. The use of such databases depends on the validity and careful selection of data-sets needed for addressing the research question [73]. This is particularly the case for safety studies in the paediatric population, for which experimental data is scarce, and there is a need for building pharmacoepidemiological research capacity and support in the area of drug utilisation, safety, and effectiveness [74]. Databases play an important role in drug safety research because of their large sample sizes, flexibility in design, and research on them can be rapid and inexpensive [75]. The spontaneous reporting system provides on-going large-scale surveillance in the “real world” setting, particularly for safety signals from

populations not studied in clinical trials. It is therefore an important tool for safety signal detection. Reports collected over a reasonable period of time have proven to be very useful [76]. The importance of national ADR data has been emphasised, with a call for ADRs in databases to be regularly analysed because they represent a true picture of ADRs experienced by patients of a particular population [77]. This call underscores the importance of regular analyses of ADR data for each country due to different drugs being used, as well as a difference in incidence and prevalence of diseases.

In Europe, descriptive analyses have been performed on ADR reports in national pharmacovigilance databases, and ADRs have been characterised in children [78-81], as well as in the general population [82-84]. Adverse drug reactions experienced by children in Latin America have also been characterised [50], and a regional ADR database in India has been studied [85].

2.2 AIM

The aims of this chapter were to review the literature of descriptive studies on adverse drug reactions in children separately and children and adults combined (general population) in regional, national and international pharmacovigilance databases and:

- Identify most commonly reported ADRs
- Identify most commonly reported drugs
- Determine drug causality assessment for the ADRs
- Determine number of fatalities
- Determine notifiers of ADRs

- Evaluate differences between countries in relation to ADRs and success of reporting scheme

2.3 LITERATURE SEARCH

In order to capture the relevant articles, search terms as ‘adverse drug reaction*, adverse effect*, adverse event*, side effect*, pharmacovigilance, spontaneous reporting, drug surveillance program, adverse drug reaction reporting system and adverse drug reaction reporting were used (Table 2.1). Only articles which retrospectively described adverse drug reactions for children and the general population from national, international or regional pharmacovigilance databases were considered. Studies describing ADRs on specific drugs, vaccines, herbal/complementary medicines, medication errors, specific treatments and procedures for disease conditions were excluded. All ADR studies outside of national, international or regional pharmacovigilance databases were also excluded.

The databases used were PubMed, Embase and MEDLINE. The PubMed database was searched from when the International drug monitoring centre was established in 1978 to March 2015. Embase and MEDLINE were searched from 1980 to March 2015 and 1947 to March 2015 respectively. Google Scholar was also searched for relevant articles. In addition to these searches, the reference lists of publications were also searched. The search strategy is as shown below in Table 2.1.

Table 2. 1: Search strategy for articles

Database	Step	Search Terms
PubMed	1	Adverse drug reaction*
	2	Adverse effect*
	3	Side effect*
	4	1 OR 2 OR 3
	5	Pharmacovigilance
	6	Spontaneous reporting
	7	Adverse drug reaction reporting system
	8	5 OR 6 OR 7
	9	4 AND 8
Embase/MEDLINE	1	Adverse drug reaction*
	2	Adverse effect*
	3	Adverse event*
	4	Side effect*
	5	1 OR 2 OR 3 OR 4
	6	Pharmacovigilance
	7	Drug surveillance program
	8	Adverse drug reaction reporting
	9	Adverse event reporting
	10	6 OR 7 OR 8 OR 9
	11	5 AND 10

2.4 SUMMARY OF FINDINGS

A total of 40 articles were identified from PubMed, Embase and MEDLINE, and one relevant article from Google Scholar, which brought the total number of studies included for the review to 41 (Figure 2.1).

Articles from PubMed, Embase and MEDLINE

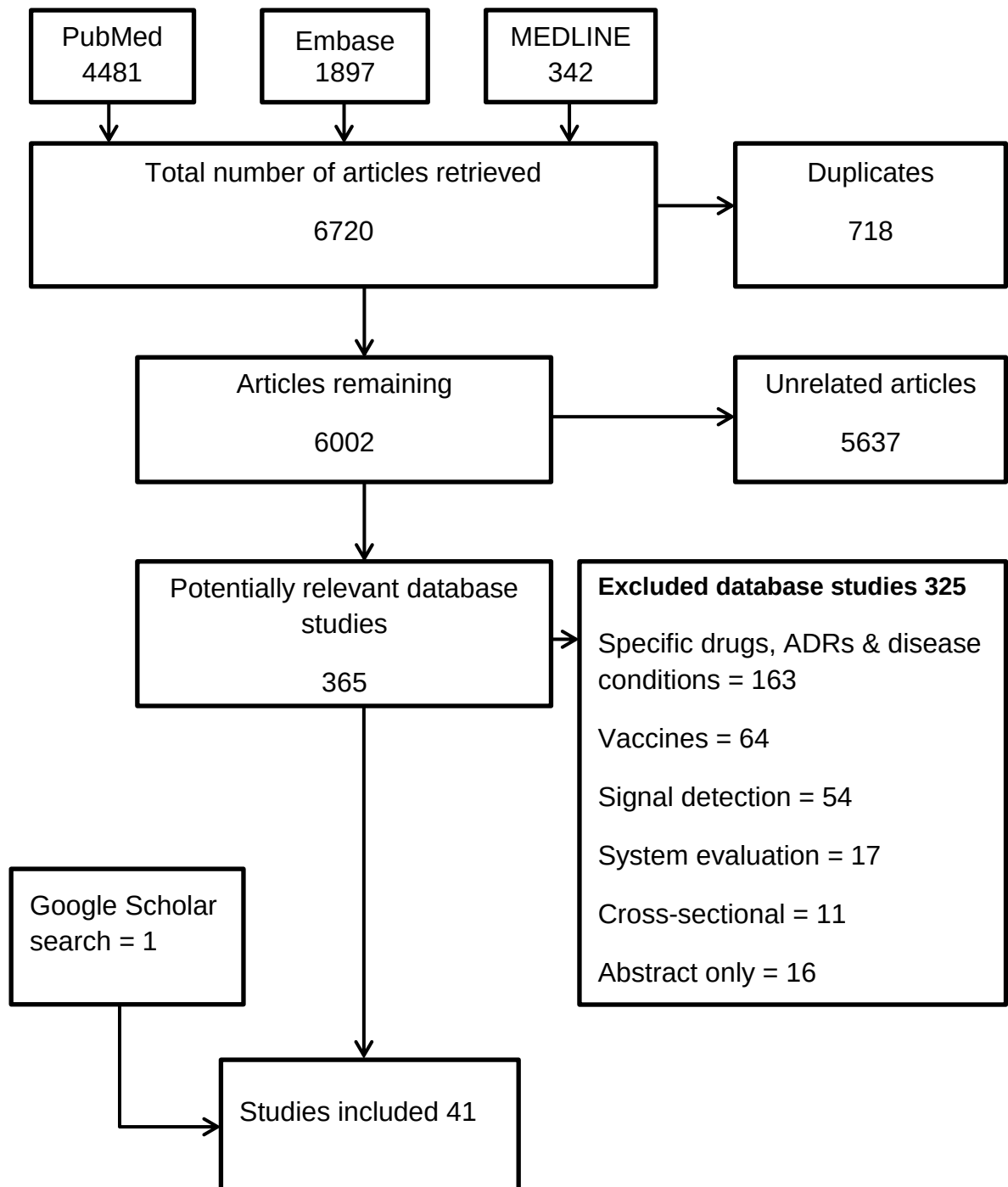


Figure 2. 1: Flow chart of literature search and studies included

Out of the 41 articles identified, 21 were studies on the general population and 20 were paediatric studies. The studies identified were made up of serious/fatal ADRs (4), patient/consumer reports (3), nurses' reports (2), and 32 of the studies were general reports. The earliest study on the general population was conducted from the Italian pharmacovigilance database and published in 1999. The earliest report on paediatric ADRs was from the Spanish pharmacovigilance database published in the year 2000.

The majority of studies grouped the ADRs in system organ class (SOC) and suspect drugs in anatomical therapeutic class (ATC), and presented them in percentages of the first, second and third most frequently reported. The type of notifiers, causality assessment criteria of the drugs and death reports were also presented in percentages.

2.5 DESCRIPTION OF STUDIES

The articles identified included 3 studies conducted from the Worldwide ADR database, Vigibase, and one from the European ADR database, EudraVigilance. The data sources for these studies are termed 'International' in this review. The majority of the studies were conducted in Europe, and only one study was identified in Africa (Figure 2.2).

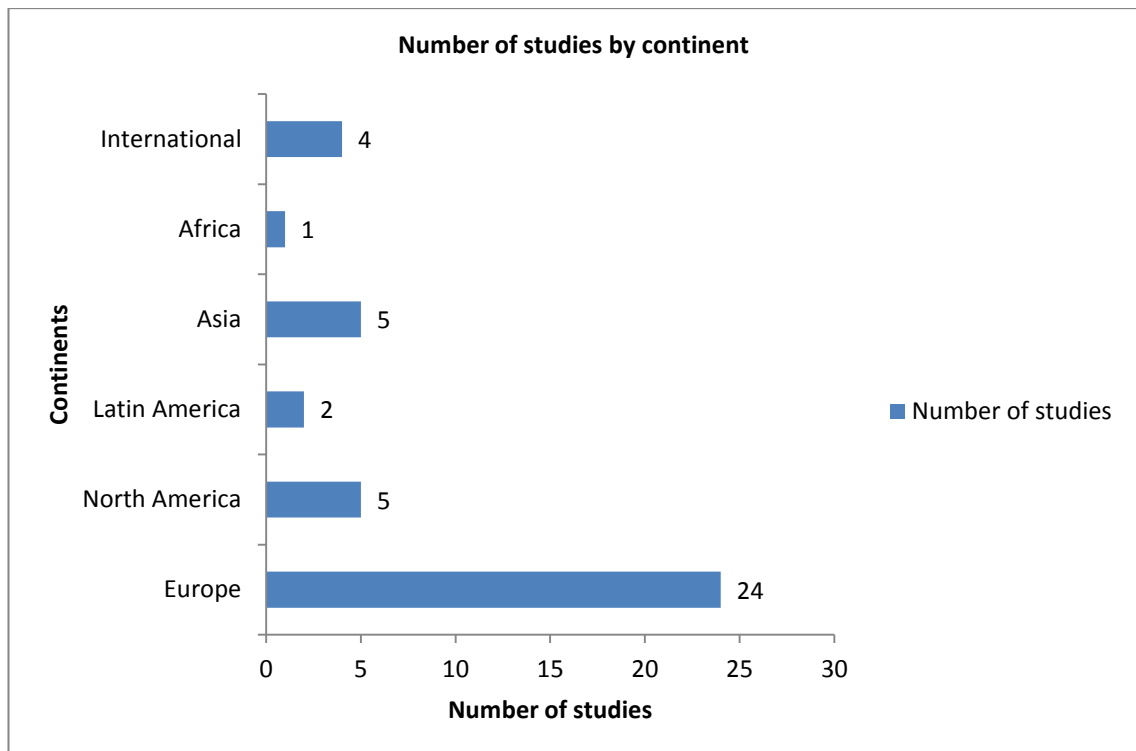


Figure 2. 2: Continents and number of National database studies

Of the 21 studies identified for the general population, two-thirds were conducted in Europe. There were 4 studies from Asia, but only one each from Africa and North America. There were 9 regional and 11 national studies (Table 2.2). The duration of collected data studied ranged from 1 – 16 years with a mean duration of 5 years. National ADR reporting rates were not described in the reports. These were calculated using general population estimates of the countries from United Nations Population Division [86] for the year of study.

[Reporting rate = annual average number of reports/population X 1 million]
(Table 2.2)

Table 2. 2: Type of study and Annual reporting frequency for the general population

Author/continent	Country	Study duration (years)	Number of reports	Percentage of serious reports/ADRs	Population estimate*	ADR Reporting rate	description of reports/ source of data
International							
Aagaard et al. 2012 [87]	International	10	1359067	16	7.1 billion	19	VigiBase study
Europe							
Marques et al. 2014 [88]	Portugal	10	3154	56	10.6 million	30	Regional study
Motola et al. 2014 [89]	Italy	10	9631	27	61.1 million	16	Regional study
Giofre et al. 2013 [90]	Italy	1	461	16	61.0 million	8	Regional study
Scicchitano et al.2012 [91]	Italy	1	138	55	60.9 million	2	Regional study
Conforti et al. 2012 [84]	Italy	6	1403	23	60.9 million	4	National study (Nurses' reports only)
Kopečna et al. 2011 [83]	Czech Republic	5	7708	74	10.6 million	145	National study
McLernon et al. 2010 [82]	UK	2	26129	-	62.0 million	210	National study
Aagaard et al. 2009 [58]	Denmark	3	544	46	5.5 million	33	National study (Consumer reports only)
Leone et al. 2008 [92]	Italy	6	450	-	59.8 million	1	National study (Fatal reports only)
De Langen et al. 2008 [93]	Netherlands	3	2522	20	16.5 million	60	National study (Consumer reports only)
Ulfvarson et al.2007 [94]	Sweden	2	912	8	**9.0 million	50	National study (Nurses' reports only)
Wester et al. 2007 [95]	Sweden	10	31859	-	9.0 million	348	National study (Fatal suspected ADRs only)
Thiessard et al. 2005 [96]	France	16	197580	45	61.4 million	201	National study
Cutroneo et al. 1999 [97]	Italy	2	284	32	56.9 million	2	Regional study
Asia							
Kalaiselvan et al. 2014 [98]	India	2	4357	26	1.3 billion	2	Regional study
Jha et al. 2012 [99]	Nepal	3	113	-	27.5 million	1	Regional study
Shin et al. 2009 [51]	Korea	1	1303	16	48.2 million	27	Regional study
Jose et al. 2006 [52]	India	1	382	-	1.1 billion	3	Regional study
North America							
Moore et al. 2007 [100]	USA	8	467809	-	303.7 million	192	National study (Serious adverse events only)
Africa							
Ermias et al. 2011 [101]	Ethiopia	6	249	-	89.4 million	0.5	National study

*Population estimates were taken from United Nations Population Division, *World Population Prospects: The 2012 Revision* [86] to calculate the reporting rates

**Population as reported in study

The highest ADR reporting rate was recorded in a Swedish study which described data collected for a period of 10 years [95]. The study conducted in Africa had the lowest reporting rate of 0.5 reports per million individuals per year [101]. The seriousness of the events was reported in percentages of ADRs or reports, and this ranged between 8 – 74% of the total number of ADRs or reports described.

The 20 studies which described ADRs in children are shown in Table 2.3. Half of the studies identified were from Europe. The age of the children studied ranged from 0 ≤ 19 years. The period of time data was collected for the studies in North America ranged from 3 – 5.7 years, and 3 – 37 years in the European studies. For the studies which described seriousness of the events, the percentages of ADRs or reports ranged between 2 – 68% of the total number of ADRs or reports. The highest proportion of serious reports was from North America (42-62%). The 37-year data described fatal suspected ADRs submitted through the Yellow Card Scheme between 1964 and 2000 in UK. Four out of the 20 studies described reporting rates. The reporting rates for the other studies were calculated using an estimate of the childhood population for the year of study, as described for the general population studies. The highest ADR reporting rates were seen in regional studies conducted in Cuba. In Europe, ADR reporting rates were higher in the UK, Denmark and Sweden, and in the USA, a reporting rate of 255 reports per million children per year was reported for a study conducted on children aged less than 2 years.

Table 2. 3: Type of study and Annual reporting frequency for children

Author/continent	Country	Children Population (years)	Study duration (years)	Number of reports	Percentage of serious reports/ADRs	Population estimate*	ADR reporting rate	Source of data/ description of reports
International								
Aagaard et al. 2014 [102]	International	≤ 17	5	240	68	2.2 billion	0.02	VigiBase (Consumer reports)
Star et al. 2011 [103]	International	≤ 17	10	268145	-	2.2 billion	12	VigiBase
Europe								
Blake et al. 2014 [104]	International	< 18	18.5	279359	-	742.8 million	20	EudraVigilance (European study)
Ferrajolo et al. 2014 [105]	Italy	< 18	12	8338	39	10.3 million	67	National study
Carnovale et al. 2014 [106]	Italy	≤ 17	4	3539	17	10.3 million	86	Regional study
Aldea et al. 2012 [107]	Spain	≤ 17	6	4279	37	8.4 million	85	National study
Hawcutt et al. 2012 [78]	UK	< 17	10	31726	-	13.3 million	238	National study
Aagaard et al. 2010 [79]	Denmark	≤ 17	10	2437	42	**1.1 million	**222	National study
Kimland et al. 2005 [80]	Sweden	≤ 15	15	5771	13	**1.7 million	**226	National study
Schirm et al. 2004 [108]	Netherlands	≤ 16	7	773	7	3.6 million	31	National study
Clarkson et al. 2004 [109]	UK	≤ 16	3	456	33	13.2 million	11	Regional study
Clarkson et al. 2002 [110]	UK	≤ 14	37	43755	-	11.0 million	107	National study (Fatal ADR reports only)
Morales-Olivas et al. 2000 [81]	Spain	≤ 14	10	1419	27	5.9 million	24	National study
North America								
Lee et al. 2014 [111]	USA	< 18	5.7	78623	42	75.2 million	183	National study
Johann-Liang et al. 2009 [37]	USA	< 18	5	36241	62	75.1 million	97	National study
Carleton et al. 2007 [30]	Canada	≤ 19	4.5	1193	61	7.0 million	38	National study
Moore et al. 2002 [112]	USA	< 2	3	5976	61	7.8 million	255	National study; children < 2 years
Latin America								
Arencibia et al. 2012 [113]	Cuba	≤ 18	2	533	31	**183,105	**1458	Regional study
Arencibia et al. 2010 [50]	Cuba	≤ 18	1	124	15	**195,504	**634	Regional study
Asia								
Li et al. 2014 [114]	China	≤ 17	1	3848	2	301.2 million	13	Regional study

*Population estimates were taken from United Nations Population Division, World Population Prospects: The 2012 Revision [86] to calculate the reporting rates

**Population and rate as reported in study

2.5.1 Notifiers of ADRs

Five studies conducted in Europe were on ADRs submitted by specific notifiers. Four of these were on ADRs in the general population reported by nurses (2) and consumers (2). The 5th study was on paediatric ADRs reported by consumers in Vigibase. There were no studies from specific notifiers of ADRs in the other continents.

Sixteen studies described notifiers of ADRs (Table 2.4) – general population (7) and children (8). Doctors were the largest group of reporters in all the studies and pharmacists the second. Nurses were most likely to submit reports in Portugal, Cuba and Ethiopia. Other HCPs submitted reports in countries in Europe, North America, Latin America and Asia. The largest proportion of reports from consumers was from the USA.

Table 2. 4 Notifiers of reports

Author/continent	Country	Physicians/doctors (%)	Pharmacists (%)	Nurses (%)	Other HCPs (%)	Consumers (%)	Comments
General population studies							
Europe							
Marques et al. 2014 [88]	Portugal	54	32	15	-	-	Regional
Motola et al. 2014 [89]	Italy	90	2	1	-	1	Regional
Giofre et al. 2013 [90]	Italy	87	-	-	-	-	Regional
Scicchitano et al. 2012 [91]	Italy	97	-	-	-	-	Regional
Kopečna et al. 2011 [83]	Czech Republic	53	1	-	10	1	National
Thiessard et al. 2005 [96]	France	91	5	-	3	-	National
Africa							
Ermias et al. 2011 [101]	Ethiopia	76	2	6	16	-	National
Children studies							
International							
Star et al. 2011 [103]	International	55	3	-	3	4	VigiBase reports
Europe							
Ferrajolo et al. 2014 [105]	Italy	83	10	2	4	1	National
Aldea et al. 2012 [107]	Spain	63	11	-	24	-	National
Hawcutt et al. 2012 [78]	UK	Not specified	5 – 8	41.8	Not specified	Not specified	National
Aagaard et al. 2010 [79]	Denmark	89	1	-	7	4	National
Latin America							
Arencibia et al. 2012 [113]	Cuba	73	15	9	1	1	Regional
Arencibia et al. 2010 [50]	Cuba	60	16	6	18	-	Regional
Asia							
Li et al. 2014 [114]	China	52	24	-	16	3	Regional
North America							
Lee et al. 2014 [111]	USA	31	6	-	22	31	National

2.5.2 Reported ADRs

Skin and nervous system disorders were the most frequent ADRs in the majority of the studies in the general population (Table 2.5). Other common ADRs were GIT disorders, in particular nausea, vomiting and diarrhoea. The less commonly reported ADRs included dizziness, constipation and leukopenia.

The majority of the studies in the children population also reported skin disorders as the most frequent ADRs (Table 2.6). Other common ADRs were nervous system disorders (headache, dizziness and drowsiness), and pyrexia/fever. The less commonly reported ADRs were convulsion, diarrhoea and agitation.

Two studies on the general population [92, 95] and one on children [110] described only fatal ADRs. A study conducted on the general population in Denmark [58] reported only serious ADRs. The most frequent fatal ADRs in children and adults were hepatic failure and haemorrhage respectively.

Table 2. 5: Most frequently reported ADRs (general population)

Author/continent	Country	1 st most frequent ADR	2 nd most frequent ADR	3 rd most frequent ADR	Comments
International					
Aagaard et al. 2012 [87]	International	General disorders (15%)	Skin disorders (14%)	Nervous disorders (12%)	
Europe					
Marques et al. 2014 [88]	Portugal	Skin disorders (21%)	General disorders (20%)	Gastrointestinal disorders (15%)	
Giofre et al. 2013 [90]	Italy	Skin disorders (29%)	Gastrointestinal disorders	Lack of efficacy	
Conforti et al. 2012 [84]	Italy	Skin disorders (56%)	General disorders (19%)	Gastrointestinal disorders (17%)	
McLernon et al. 2010 [82]	UK	Nausea	Headache	Vomiting	
Aagaard et al. 2009 [58]	Denmark	Nervous disorders (20%)	General disorders (13%)	Gastrointestinal disorders (12%)	Serious ADRs only
Leone et al. 2008 [92]	Italy	Blood and bone marrow dysfunction (16%)	Haemorrhages (14%)	Anaphylactic shock (14%)	Fatal reports only
De Langen et al. 2008 [93]	Netherlands	Myalgia (3.6%)	Fatigue (3.2%)	Headache (2.9%)	
Ulfvarson et al. 2007 [94]	Sweden	Skin reactions (45%)	Common vaccine symptoms (31%)	Gastrointestinal disorders (6%)	
Wester et al. 2007 [95]	Sweden	Haemorrhages (61%)	Blood and bone marrow dysfunction (7%)	Liver dysfunction (4%)	Fatal reports only
Thiessard et al. 2005 [96]	France	Skin disorders (29%)	Nervous disorders (19%)	Gastrointestinal disorders (12%)	
Cutroneo et al. 1999 [97]	Italy	Skin disorders (28%)	Gastrointestinal disorders (17%)	General disorders (15%)	
Asia					
Kalaiselvan et al. 2014 [98]	India	Vomiting (6%)	Diarrhoea (5%)	Constipation (4%)	
Jha et al. 2012 [99]	Nepal	Maculopapular rash (22%)	Vomiting (17%)	Diarrhoea 12%	
Shin et al. 2009 [51]	Korea	Skin disorders (42%)	Nervous disorders (14%)	Gastrointestinal disorders (13%)	
Jose et al. 2006 [52]	India	Rash (11%)	Vomiting (7%)	Leukopenia (6%)	
Africa					
Ermias et al. 2011 [101]	Ethiopia	Skin disorders (34%)	Nervous disorders (29%)	Cardiovascular disorders (15%)	

Note: ADRs in order of frequencies and percentages are as reported in the studies

Table 2. 6: Most frequently reported ADRs (children)

Author	Country	1 st most frequent ADR	2 nd most frequent ADR	3 rd most frequent ADR	Comments
International					
Aagaard et al. 2014 [102]	International	General disorders (20%)	Nervous system disorders (14%)	Injury, poison & proc compl (7%)	VigiBase data
Star et al. 2011 [103]	International	Skin disorders (35%)	General disorders (20%)	Nervous system disorders (19%)	VigiBase data
Europe					
Blake et al. 2014 [104]	International	Pyrexia (13%)	Vomiting (6%)	Convulsion (4%)	EudraVigilance data
Ferrajolo et al. 2014 [105]	Italy	Skin disorders (52%)	Gastrointestinal disorders (17%)	Nervous system disorders (12%)	
Carnovale et al. 2014 [106]	Italy	Skin disorders (26%)	General disorders (24%)	Gastrointestinal disorders (11%)	
Aldea et al. 2012 [107]	Spain	Pyrexia (7%)	Application site reaction (4%)	Urticaria (3%)	
Hawcutt et al. 2012 [78]	UK	Headache (10%)	Dizziness (9%)	Pyrexia (7%)	
Aagaard et al. 2010 [79]	Denmark	General disorders (31%)	Skin disorders (18%)	Nervous system disorders (15%)	
Kimland et al. 2005 [80]	Sweden	Application site reaction (24%)	Fever (12%)	Rash (Exanthema) (7%)	
Schirm et al. 2004 [108]	Netherlands	Tooth discolouration (6%)	Rash (5%)	Agitation (3%)	
Clarkson et al. 2004 [109]	UK	Not reported	Not reported	Not reported	
Clarkson et al. 2002 [110]	UK	Hepatic failure (15%)	Bone marrow suppression (6%)	Sudden unexplained death (5%)	Fatal ADR reports only
Morales-Olivas et al. 2000 [81]	Spain	Rash (18%)	Urticaria (6%)	Diarrhoea (5.7%)	
North America					
Lee et al. 2014 [111]	USA	Not reported	Not reported	Not reported	
Johann-Liang et al. 2009 [37]	USA	Not reported	Not reported	Not reported	
Carleton et al. 2007 [30]	Canada	Not reported	Not reported	Not reported	
Moore et al. 2002 [112]	USA	Not reported	Not reported	Not reported	
Latin America					
Arencibia et al. 2012 [113]	Cuba	Urticaria/angioedema (29%)	Drowsiness (11%)	Vomiting (9%)	
Arencibia et al. 2010 [50]	Cuba	Drowsiness (14%)	Headache (11%)	Respiratory distress/failure (10%)	
Asia					
Li et al. 2014 [114]	China	Rash (Exanthema) (29%)	Fever (21%)	Application site reaction (9%)	

Note: ADRs in order of frequencies and percentages are as reported in the studies

2.5.3 Reported drugs

The majority of the studies conducted in Europe reported anti-infective agents, followed by nervous system medicines as the most frequently reported drugs (Table 2.7). All the six studies conducted in Italy described antimicrobial agents as first or second most frequently reported drugs. Amoxicillin/clavulanic acid was the individual antibiotic most frequently implicated with the ADRs in Italy. Statins were the most commonly implicated drugs for the ADRs reported by patients in The Netherlands.

Antiretroviral medications were the most frequently reported drugs in Ethiopia, and in India, anticancer drugs were most frequently implicated for the ADRs.

Table 2. 7: Most frequently reported drugs (general population)

Author/ continent	Country	1 st most frequent drug	2 nd most frequent drug	3 rd most frequent drug	4 th most frequent drug	5 th most frequent drug	Comments
International							
Aagaard et al. 2012 [87]	International	Nervous system(16%)	Cardiovascular System (13%)	Not reported	Not reported	Not reported	
Europe							
Marques et al. 2014 [88]	Portugal	Antibiotics (22%)	Vaccines (16%)	Nervous system (15%)	Musculoskeletal system (14%)	Cardiovascular system (11%)	
Motola et al. 2014 [89]	Italy	lomeprol (3%)	Amoxicillin/clavulani c acid (2%)	Lenalidomide (1.5%)	Levofloxacin (1.4%)	Atorvastatin (1.0%)	
Giofre et al. 2013 [90]	Italy	Antibacterial agents (19%)	Anti-epileptics (13%)	Antineoplastic agents (12%)	Anti-inflammatory agents (11%)	Vaccines	
Scicchitano et al. 2012 [91]	Italy	Antimicrobial agents (25%)	Anti-inflammatory agents (19%)	Vaccines	Opioids	Antineoplastic agents	
Conforti et al. 2012 [84]	Italy	Amoxicillin+clavulanic acid (10%)	Amoxicillin (5%)	Levodopa+ carbidova (4%)	Aspirin (3%)	Ketoprofen (3%)	
Kopečna et al. 2011 [83]	Czech Republic	Vaccines	Ketoprofen	Amoxicillin	Estradiol	Infliximab	
McLernon et al. 2010 [82]	UK	Nervous system	Cardiovascular system	Anti-infectives	Alimentary tract & metabolism	Musculoskeletal system	
Aagaard et al. 2009 [58]	Denmark	Nervous system (49.7%)	Cardiovascular system (10.7%)	Anti-infectives (7.3%)	Musculoskeletal system (6.9%)	Alimentary tract & metabolism (5.9%)	Serious ADRs only
Leone et al. 2008 [92]	Italy	Anti-infectives (21.9%)	Antineoplastic agents (18.8%)	Nervous system (14.8%)	Blood products (12.7%)	Musculoskeletal system (10.4%)	Fatal reports only
De Langen et al. 2008 [93]	Netherlands	Statins (8.2%)	Serotonin reuptake inhibitors (4.7)	β-Blockers (3.6%)	Anticoagulants (3.5%)	Proton pump inhibitors (3.4%)	Patient reports only
Ulfvarson et al. 2007 [94]	Sweden	Vaccines (87%)	Destogestrel (4%) (contraceptive)	Lidokain (2%) (local anesthetics)	Warfarin (2%) (anticoagulant)	Simvastatin (1%)	
Wester et al. 2007 [95]	Sweden	Vitamin K antagonists (44.5%)	Acetylsalicylic acid (7.6%)	Fibrinolytics (7.4%)	Heparins (7.2%)	Oestrogen containing drugs (2.1%)	Fatal reports only
Thiessard et al. 2005 [96]	France	Nervous system (23%)	Cardiovascular system (19%)	Anti-infectives (17%)	Alimentary tract & metabolism (11%)	Not reported	
Cutroneo et al. 1999 [97]	Italy	Acetylsalicylic acid (11.3%)	Lomefloxacin (4.6%)	Ceftriaxone (3.9%)	Diclofenac (3.2%)	Piroxicam (2.5%)	

Note: Drugs and drug classes in order of frequencies and percentages are as reported in the studies

Table 2.7: Most frequently reported drugs (general population) Continued

Author/continent	Country	1 st most frequent drug	2 nd most frequent drug	3 rd most frequent drug	4 th most frequent drug	5 th most frequent drug	Comments
Asia							
Kalaiselvan et al. 2014 [98]	India	Cisplatin (6.5%)	Carboplatin (4.4%)	Cyclophosphamide (3.4%)	Asetylsalicylic acid (2.6%)	Insulin (2.5%)	
Jha et al. 2012 [99]	Nepal	Antimicrobials (45.1%)	Antihypertensives (31.3%)	NSAIDs (11.5%)	Proton pump inhibitors (4.4%)	Corticosteroids (4.4%)	
Shin et al. 2009 [51]	Korea	Antibiotics (31.6%)	Contrast dye (14.0%)	NAISDs (11.1%)	Antipsychotics (5.4%)	Anticonvulsants (5.2%)	
Jose et al. 2006 [52]	India	Phenytoin (7.8%)	Cyclophosphamide (6.9%)	Doxorubicin (4.9%)	Amoxicillin (3.4%) Prednisone (3.4%)	Methotrexate (2.9%)	
Africa							
Ermias et al. 2011 [101]	Ethiopia	Antiretrovirals (70.6%)	Antibiotics (17.5%)	Antituberculosis (2.8%)	Antifungals (2.4%)	Analgesics (1.6%)	

Note: Drugs and drug classes in order of frequencies and percentages are as reported in the studies

The most frequently reported drugs for children are shown in Table 2.8. Antibiotics and vaccines were the most frequently reported drugs in almost all the studies identified in Europe, Latin America and Asia. Drugs used for treating attention deficit hyperactivity disorders (ADHD) and isotretinoin were mostly implicated in North America. In one of the studies identified in USA, methylphenidate medication were the most frequently reported for children less than 12 years old, and children aged 12 to <18 years experienced more ADRs with isotretinoin. This reflects the common groups of drugs used in these age groups in these countries.

Table 2. 8: Most frequently reported drugs (children)

Author/ continent	Country	1 st most frequent drug	2 nd most frequent drug	3 rd most frequent drug	4 th most frequent drug	5 th most frequent drug	Comments
International							
Aagaard et al. 2014 [102]	International	Anti-infectives (36%)	Antineoplastic agents (23%)	Sex hormones (13%)	Nervous system (12%)	Respiratory system (2%)	VigiBase
Star et al. 2011 [103]	International	Amoxicillin (33%)	Atomoxetine (28%)	Dermatologicals (12%)	Respiratory system (11%)	Alimentary tract & metabolism (10%)	VigiBase
Europe							
Blake et al. 2014 [104]	International	Vaccines	Isotretinoin	Methylphenidate	Etanercept	Paracetamol	Eudra- Vigilance
Ferrajolo et al. 2014 [105]	Italy	Amoxicillin/ clavulanic acid	Amoxicillin	Ibuprofen	Paracetamol	Clarithromycin	Reports exclude vaccines
Carnovale et al. 2014 [106]	Italy	Vaccines (37.5%)	Antibacterials (21.6%)	Antineoplastic agents (9.5%)	Psycholeptics (6.7%)	Anti-inflammatory (5.0%)	
Aldea et al. 2012 [107]	Spain	Vaccines	Methylphenidate	Respiratory system		Not reported	
Hawcutt et al. 2012 [78]	UK	Vaccines	ADHD medication & melatonin	Anti-epileptics	Anti-infectives excl vaccines	Immunosuppressants & chemotherapy excl steroids	
Aagaard et al. 2010 [79]	Denmark	Vaccines (61.1%)	Antidepressants (6.9%)	Antiepileptics (4.0%)	Allergens (3.0%)	Antipsychotics (2.6%)	
Kimland et al. 2005 [80]	Sweden	Vaccines (63.8%)	Antibacterials (10.1%)	Antiasthmatics (4.9%)	Antiepileptics (3.1%)	Not reported	
Schirm et al. 2004 [108]	Netherlands	Amoxicillin (5%)	Salbutamol (3.2%)	Clarithromycin (2.8%)	Methylphenidate (2.7%)	Fluticasone (2.7%)	
Clarkson et al. 2004 [109]	UK	Vaccines (34.7%)	Topical local anaesthetics (17.2%)	Anticonvulsants (11.0%)	Antibiotics (9.1%)	Cytotoxics & immunosuppressants (5.5%)	
Clarkson et al. 2002 [110]	UK	Anticonvulsants (20.0%)	Cytotoxics (10.8%)	Antibiotics (7.9%)	Anaesthetics- intravenous (5.1%)	Anaesthetics-inhaled (4.4%)	Fatal reports only
Morales-Olivas et al. 2000 [81]	Spain	Vaccines (12.9%)	Amoxicillin (8.5%)	Erythromycin (3.7%)	Cotrimoxazole (3.0%)	Acetylsalicylic acid (2.7%)	

Note: Drugs and drug classes in order of frequencies and percentages are as reported in the studies

Table 2.8: Most frequently reported drugs (children) continued

Author/continent	Country	1 st most frequent drug	2 nd most frequent drug	3 rd most frequent drug	4 th most frequent drug	5 th most frequent drug	Comments
North America							
Lee et al. 2014 [111]	USA	Methylphenidate (3.5%)	Montelukast (1.9%)	Ibuprofen (1.5%)	Lisdexamfetamine (1.3%)	Somatropin (1.2%)	Children 1 to <12 years
Lee et al. 2014 [111]	USA	Isotretinoin (3.2%)	Infliximab (2.8%)	Drospironone & ethinyl estradiol (1.7%)	Methylphenidate (1.6%)	Adalimumab (1.3%)	Children 12 to <18 years
Johann-Liang et al. 2009 [37]	USA	ADHD drugs	Anticonvulsants	Antidepressants	Antipsychotics	Chemotherapeutics	
Carleton et al. 2007 [30]	Canada	Isotretinoin (3.8%)	Paroxetine (2.9%)	Methylphenidate (2.8%)	Amoxicillin (2.7%)	Valproic acid (2.2%)	
Moore et al. 2002 [112]	USA	Palivizumab (27.9%)	Cisapride (4.0%)	Indomethacin (3.8%)	Nitric oxide (3.4%)	Azithromycin (2.1%)	Only drugs associated with serious or fatal outcome; children < 2 years
Latin America							
Arencibia et al. 2012 [113]	Cuba	Vaccines	Antibiotics	Antihistamines	Analgesics (nonopioid)	Bronchodilators	
Arencibia et al. 2010 [50]	Cuba	Antibiotics (32%)	Vaccines (15%)	Analgesics (14%)	ACE inhibitors (6%)	Bronchodilators (6%)	
Asia							
Li et al. 2014 [114]	China	Vaccines (42.2%)	Cefuroxime (9.9%)	Azithromycin (8.8%)	Cefotiam (3.4%)	Not reported	

Note: Drugs and drug classes in order of frequencies and percentages are as reported in the studies

2.5.4 Causality assessment of drugs

Only eight articles from Europe and Asia described causality assessment of drugs in the general population studies. Causality assessment in these studies was performed according to WHO criteria (Box 1.3). The studies conducted in Italy made up two-third of the studies identified in Europe (Table 2.9). The ADRs which were assessed with a causality criteria of 'probable' were generally more than the ones assessed as 'possible' in the eight studies identified.

Table 2. 9: Causality assessment of drugs (general population)

Author/ continent	Country	Certain (%)	Probable (%)	Possible (%)	Unlikely (%)	Comments
Europe						
Marques et al. 2014 [88]	Portugal	6	67	20	1	
Motola et al. 2014 [89]	Italy	3	39	53	5	
Conforti et al. 2012 [84]	Italy	1	76	-	-	Nurses' reports only
Leone et al. 2008 [92]	Italy	-	50	50	-	Fatal reports only
Wester et al. 2007 [95]	Sweden	<1	19	78	<1	
Asia						
Jha et al. 2012 [99]	Nepal	-	60	40	-	
Shin et al. 2009 [51]	Korea	14	46	32	-	
Jose et al. 2006 [52]	India	1	54	44	1	

The proportion of ADRs which were related to drugs for the causality criteria of 'probable' ranged between 19 – 76% in Europe, and ranged between 46 – 60% in studies conducted in Asia. Few ADRs were assessed as 'certain' and 'unlikely' related to the drugs.

Drug causality assessment was reported in only 3 paediatric studies. Arencibia and colleagues reported causality criteria of 'probable' in 84% (2010) [50], and 95.5% (2012) [113] of the paediatric ADRs in Cuba. Morales-Olivas and colleagues (2000) [81] in Spain reported 93.2% of the paediatric ADRs were assessed with causality criteria of 'probable/possible'.

2.5.5 Deaths reported

Fourteen out of the 21 studies identified for the general population reported proportion of deaths (Table 2.10). One of the studies identified in Europe described only fatal reports.

Table 2. 10: Death reports (general population)

Authors/continent	Country	Number of patients	Number of deaths	Proportion of deaths (%)	Comments on type of data
Europe					
Marques et al. 2014 [88]	Portugal	3154	19	1.1	
Motola et al. 2014 [89]	Italy	9631	124	1.3	
Scicchitano et al.2012 [91]	Italy	138	2	1.4	
Kopečna et al. 2011 [83]	Czech Republic	7708	162	2.1	
McLernon et al. 2010 [82]	UK	5180	36	0.7	
Leone et al. 2008 [92]	Italy	450	450	100	Fatal reports only
De Langen et al. 2008 [93]	Netherlands	2522	32	0.6	
Wester et al. 2007 [95]	Sweden	31859	990	3.1	
Thiessard et al. 2005 [96]	France	197580	7508	3.8	
Cutroneo et al. 1999 [97]	Italy	284	4	1.4	
Asia					
Kalaiselvan et al. 2014 [98]	India	4357	8	0.7	
Shin et al. 2009 [51]	Korea	1418	34	2.4	
Jose et al. 2006 [52]	India	382	1	0.2	
North America					
Moore et al. 2007 [100]	USA	467809	80880	17.3	Serious ADRs only

The proportion of deaths for the 9 European studies ranged from 0.6 – 3.8%. In the French study which reported 3.8% fatality rate, 1.5% of the patients died because of ADRs, 1.2% died possibly of ADRs, and non-ADR related causes were linked with 1.1% of patients who died. The number of deaths recorded may be attributed to selective reporting of fatal ADRs. The proportion of reported deaths in the three Asian studies ranged between 0.2 to 2.4%. The only study conducted in North America described serious adverse events submitted to the US Food and Drug Administration between 1998 and 2005, in which 17.3% of the patients died.

The proportion of deaths seen within reports for the paediatric studies are shown in Table 2.11.

Table 2. 11: Death reports (children)

Author/continent	Country	Number of reports	Number of deaths	Proportion of deaths (%)	Comments on type of data
International					
Aagaard et al. 2014 [102]	International	240	3	1.3	VigiBase (Consumer reports)
Europe					
Ferrajolo et al. 2014 [105]	Italy	8338	28	0.3	
Aldea et al. 2012 [107]	Spain	4279	33	0.8	
Aagaard et al. 2010 [79]	Denmark	2437	28	1.1	
Kimland et al. 2005 [80]	Sweden	5771	8	0.1	
Clarkson et al. 2004 [109]	UK	456	10	2.2	
Clarkson et al. 2002 [110]	UK	43755	331	0.8	Fatal ADR reports only (37-year data)
Morales-Olivas et al. 2000 [81]	Spain	1419	4	0.3	
North America					
Lee et al. 2014 [111]	USA	78623	6290	8.0	
Johann-Liang et al. 2009 [37]	USA	36241	2901	8.0	
Carleton et al. 2007 [30]	Canada	1193	41	3.4	
Moore et al. 2002 [112]	USA	7111	769	13.0	3-year data
Latin America					
Arencibia et al. 2012 [113]	Cuba	533	1	0.2	
Arencibia et al. 2010 [50]	Cuba	124	2	1.6	
Asia					
Li et al. 2014 [114]	China	3848	13	0.3	

The studies conducted in North America reported the highest fatality rates which range from 3.4 – 13.0%. These rates contrasted sharply with the rates reported in Europe, which ranged between 0.1 – 2.2% with a mean rate of 0.8%.

2.6 DISCUSSION

2.6.1 ADR studies

The reporting of ADRs is in its early stages of development in Africa and Asia, compared to high income countries in Europe and North America. There have been very few published studies from national pharmacovigilance databases in these continents and this lack of published studies may be attributed to insufficient reports in the databases, or lack of knowledge on the importance of this aspect of pharmacovigilance. As at 25 February 2015, 120 countries have registered as full members of WHO Programme for International Drug Monitoring [115]. The earliest member country in Asia was Malaysia in 1990 and from Africa, Morocco and South Africa became members in 1992. Nigeria [116] and Malaysia [117] publish reports of ADRs in health authority newsletters and bulletins. However, these reports are not available in the literature, and the ADR status in these countries is not generally known worldwide.

2.6.2 Reporting rate

The countries which have established programmes of ADR reporting in their healthcare system are likely to have more reports in National ADR databases. The size of the country, population and duration of time of data collected for the study may also influence the number of reports in the database. The combination of these factors may have contributed to the higher number of reports or rates of reporting per population observed in France [96] and USA [100, 111]. The high number of reports received per

year is also an indication of success of the reporting scheme for that country. This was observed in the national paediatric studies conducted in UK by Hawcutt and colleagues [78], in USA [112], and in Cuba [50, 113]. In the study conducted in Africa [101], ADR reports were few and indicate improvement is needed in their pharmacovigilance systems.

2.6.3 Notifiers of ADRs

Even though most of the studies in Europe and North America showed evidence of efficient reporting scheme, not all the HPCs were actively engaged in reporting ADRs. The results showed physicians/doctors submitted more reports than pharmacists and nurses. This is understandable due to their clinical background and knowledge of pharmacology of the drugs. Other HCPs, especially nurses, could be encouraged by giving them focussed education to detect and report ADRs [118], due to their unique role in observing patients' signs and symptoms. This approach has contributed approximately 12% of all ADR reported in Sweden [94]. Nurses reported most of the ADRs in UK [78].

In Nigeria [119] and Ghana [120], research has shown that lack of reporting forms and fear of indictment on the part of reporters of ADRs [121] contribute to low level of ADR reporting. ADR reporting could be improved through awareness campaign amongst HCPs and the provision of necessary tools required for reporting ADRs. In Latin America, emphasis on pharmacovigilance during training of HCPs has been proposed as an approach which could improve ADR reporting levels [50].

2.6.4 Deaths reported

The proportions of deaths in the reports were higher in North America compared with those in Europe, Asia and Latin America for both general and paediatric studies. This may reflect differences in the use of medicines and also differences in attitudes towards reporting. Further research is needed in this area.

2.6.5 Reported drugs and ADRs in the general population

Anti-infectives for systemic use were the most frequently reported drugs in the general population. In the African study, antiretroviral drugs were implicated with the majority of the reported ADRs [101]. This may reflect the high prevalence of HIV in the country studied.

Nervous system drugs were the second most frequently reported in Europe, and were mostly reported for nausea in the UK [82], and skin disorders in France [96]. The drug-ADR pair was different in the Denmark study [58], where the most frequently reported medicines by patients were nervous system drugs and the most common ADRs were nervous disorders.

The majority of the studies described ADRs in system organ class and not in lowest level reaction terms. Skin disorders were most frequently reported in the general population studies, including the one identified from Africa.

Two studies conducted in UK and The Netherlands described the lowest level reaction terms, and not classed into system organs. Patients/consumers and HCPs in the UK study [82] reported nausea as the most frequent ADR, and nervous system drugs as the most common. The reason for the high

number of nausea cases experienced by patients could not be determined. In the Dutch study [93], patients who reported myalgia, as the most frequent ADRs, most often implicated statins. Statin – related myalgia is difficult to diagnose and is probably not recognised by many doctors. More clinical trials on statin-myalgia have been suggested [122].

A few studies described only death reports. The most common cause in the study conducted in Sweden was bleeding [95], and the drugs most frequently associated were vitamin K antagonists. Fatalities resulting from CNS haemorrhages, GI haemorrhages and other fatal bleedings were responsible for 61% of all the reports. The authors reported that the high number of fatalities resulting from haemorrhages was due to drug interaction with vitamin K antagonists, found in 25% of the reports.

2.6.6 Reported drugs in children

In Europe, Asia and Latin America, systemic anti-infectives and vaccines were the group of drugs most frequently associated with ADRs. This reflects the widespread use of anti-infectives and vaccines in children [123, 124]. The high number of vaccine-related ADRs such as pyrexia [104, 125] may be connected to vaccines administered to children as part of routine national immunisation programmes. In contrast, in North America [30, 37, 111], drugs used for treating attention deficit hyperactivity disorders (ADHD) were most often associated with ADRs. The diagnosis of ADHD in children visiting outpatient clinics in USA has been on the rise since 2000 [126], majority of these cases were treated with psychostimulants, which include methylphenidate.

2.6.7 Implications for further research

Pharmacovigilance is well developed in Europe and North America. It is not therefore surprisingly that majority of the studies identified were from these two continents. Only one study conducted from the Ethiopian ADR database in Africa was identified. Therefore, a gap exists in the literature of information on National ADR status from developing countries, especially in Ghana and Nigeria where ADR databases are maintained and have not been explored.

2.6.8 Strengths and limitations

The database search was not limited to a particular year, and this enabled all relevant articles published several years ago to be reviewed. ADRs from the general population, and specifically paediatric reports, in National ADR databases from countries in Europe and North America have been analysed.

Very few studies were conducted in Asia and Africa, therefore, comparison of reported ADRs and drugs between the continents was not possible. There was no uniformity in the reports in terms of ADRs and drugs description. Some of the studies described ADRs in system organ class and others in lowest level reaction terms. The drugs were also described differently in anatomical therapeutic class and specific drugs. All these made comparison of the studies difficult.

2.7 CONCLUSIONS

- Majority of National ADR databases analysed were from Europe and North America.
- In Africa, only one study has been conducted from a National ADR database in Ethiopia.
- ADR reporting rates are higher in European countries and USA compared to countries in Asia and Africa.
- Physicians/doctors reported more ADRs compared to pharmacists and nurses.
- Vaccines were mostly associated with ADRs in European children, and in USA, drugs used for treating ADHD were most often implicated.
- In Ethiopia, majority of the ADRs were associated with antiretroviral drugs.
- USA had the highest fatality rates in both general and paediatric studies.

CHAPTER THREE

ADVERSE DRUG REACTIONS IN NIGERIAN ADULTS (18 years and above)

3.1 INTRODUCTION

The National Pharmacovigilance Centre (NPC) in Nigeria maintains an ADR database which has not been studied. It is important to compare the reports in the database with those from other national ADR databases elsewhere. In Chapter 2, the review showed only one previous study in Africa. The result of such assessments could also help in identifying possible areas for improvement. The rational use of drugs by the public, consumption of counterfeit and substandard drugs, knowledge and controlled use of herbal medicines and awareness of the importance of ADR reporting by healthcare providers can affect the overall success of the pharmacovigilance process.

3.1.1 Healthcare delivery

Nigeria is the sixth most populated country in the world with a current population estimate of 170 million, comprising of 51% males and 49% females [127]. It has a three-tier system of healthcare delivery – primary (health centres), secondary (general hospitals) and tertiary (teaching hospitals) care – which are provided by the local councils, state governments and Federal government respectively [128]. However, individuals also access private healthcare services from qualified medical and traditional medical practitioners. Patients pay for consultation, drugs and medical/surgical procedures in Nigeria. The majority of the citizens are unable to pay for

healthcare service and resort to unqualified healthcare personnel or traditional medicine healers for their health needs. Critical and worsening cases of diseases are referred from health centres to the general hospitals, and teaching hospitals depending on severity and availability of infrastructure.

3.1.2 Disease burden

The burden of disease in Nigeria is high. There is a large population of HIV/AIDs victims in the country and it is ranked second highest in the number of new HIV infections reported globally each year. The prevalence of HIV as a percentage of the population aged 15 – 49 years was 3.1%, and 240,000 people died from HIV/AIDs in 2012 [129]. Communicable diseases, maternal, perinatal and nutritional conditions accounted for an estimated 67% of all mortality in 2008 in Nigeria [130]. Malaria is responsible for 60% of outpatient visits to health facilities, and 11% of maternal deaths [131]. The exact burden of tuberculosis in Nigeria is not known. However, the World Health Organisation (WHO) estimated the incidence rate of all forms of tuberculosis at 311 per 100,000 population, prevalence at 546 per 100,000 population, and Nigeria was ranked 4th among the 22 high tuberculosis burden countries [132]. The total number of newly detected tuberculosis cases increased from 29,465 in 2001 to 97,853 by the end of 2012 [133].

In the general population (Table 3.1), cardiovascular diseases and cancer cause more deaths than infections [134].

Table 3. 1: Major causes of death in the general population [134]

Causes of death	Per 100,000 of population
Cardiovascular diseases	417
Cancer	158
Malaria	156
HIV/AIDS	115
Injuries	109
Tuberculosis in HIV-positive people	53
Tuberculosis in HIV-negative people	39.8

Maternal mortality rates are very high in Sub-Saharan Africa, including Nigeria (380 – 730 maternal deaths per 100,000 live births), compared to high income countries such as United Kingdom (12 – 23 maternal deaths per 100,000 live births) [135].

3.1.3 Drug use

Generally, drug use is influenced by such factors as drug availability, experience of prescribers, marketing influence from pharmaceutical manufacturers, health budget, communication and cultural factors [136]. It is established that rational use of drugs offers medical, social and economic benefits, as well as contributing globally to reduction in morbidity and mortality [137]. To ensure that drugs are used properly in Nigeria, the Federal Government established the National Drug Policy in 1990 [138] with the aim of developing and operating a system of rational drug use [139]. Despite the

promulgation of this policy, drugs are still being prescribed irrationally in the country, as observed in some cases where more than two drugs from the same class are prescribed at the same time to one patient [140]. However, in a national survey of rational use of drugs, jointly conducted by the Federal Ministry of Health and WHO, most household members with acute illness sought care outside the home. It was also reported in this survey that doctors prescribed medicines for two-thirds of those with acute illness, while drug sellers prescribed for 13% and pharmacists for 7% [141].

Adverse drug reactions experienced by patients may be affected by the route of drug administration. In developing countries, it is the belief that medicines can work better when given by injection. However, there is high risk of adverse events when injections are administered by inadequately sterilised equipment or poorly trained staff. Patients have contracted diseases such as hepatitis B, hepatitis C and HIV in Africa via this process [142]. However, it is not possible to ascertain if all the ADRs reported are attributed to drugs prescribed rationally, as most patients obtain their medication directly from medicine stores without prescriptions [143]. This practice makes the monitoring of ADRs a particularly difficult endeavour.

3.1.4 Counterfeit and substandard medications

A major challenge of healthcare delivery in developing countries is the presence of counterfeit and substandard medicines in the system [144, 145]. The WHO identifies a counterfeit medicine as one that is deliberately and fraudulently mislabelled with respect to identity and source [146]. It also stated that counterfeiting can apply to both branded and generic products,

and counterfeit products may include products with correct ingredients, with wrong ingredients, without active ingredients, with incorrect quantity of the active ingredient, or with fake packaging [146].

As the most populous country in Africa, Nigeria has a large emerging pharmaceutical market [147], and medications used are mostly imported, unregistered and unauthorised for use by the National Agency for Food and Drug Administration and Control (NAFDAC) [148]. This has given room for counterfeit and substandard medications to be imported [149-151]. Research has shown that not all counterfeit and substandard drugs are imported, a great number of the manufacturers of these products are based in Nigeria [152]. According to WHO, 25 percent of all medicines in developing countries are counterfeit [153]. In Nigeria and Pakistan, counterfeit medications constitute between 40 – 50 percent of all the medicines in circulation [154], and over one-third of antibiotics and antimalarials on the WHO essential drugs list in low and lower middle income countries are substandard [155].

Counterfeit and substandard medicines contribute to poor public health and affect development, especially in developing countries. Medicines consumed in these countries are either imported or manufactured locally. Manufacturers of substandard medicines may produce these medicines under inadequate controlled processes that may lead to contamination of the final product with toxic chemicals, as in the cases of diethylene glycol poisoning in India and Nigeria [156, 157].

Generally, the prevalence of counterfeit and substandard antimicrobials is high in lower income countries and lower middle-income countries in Africa

and Asia [158]. The consumption of counterfeit and substandard drugs is thought to result in significant morbidity in Nigeria [159], as well as drug resistance to anti-infective drugs [160]. In a refugee camp in Pakistan, consumption of substandard sulfadoxine/pyrimethamine contributed to a malaria epidemic [161].

The circulation of counterfeit and substandard medicines in the open market and retail outlets in Ghana [162] is also a challenge. The regulatory authority periodically monitors medicines and herbal products used in the country and take necessary actions in withdrawing identified counterfeit and substandard products, and penalise the producers and marketers [163]. This is done to reduce the incidence of adverse drug reactions which are experienced by consumers using counterfeit medicines and herbal products. The success of the pharmacovigilance process also depends on effective identification of these classes of drugs with respect to causality assessment of ADRs reported.

3.1.5 Herbal medicine use

The general perception that 'natural' or herbal products are not synthetic and therefore less harmful means that the safety element of monitoring such medicines can be overlooked [164]. There is growing concern for the safety of these classes of medicines as they have been associated with serious side effects [165], such as allergic reactions, renal failure and hepatotoxicity [166, 167]. Consequently, the World Health Organisation has developed guidelines for monitoring them [168].

In Nigeria, herbal medicines form the bulk of the medications available, and patients often use them together with western medicines. Adverse effects ranging from skin rashes, abdominal pain, vomiting, dizziness and diarrhoea [169], and induced acute renal failure [170] have been reportedly associated with them.

In a recent study of caregivers of patients with epilepsy in Nigeria, antiepileptic drugs were used along with herbal medicines and 17% of the population studied experienced adverse effects [171]. Most of these medicines have not been evaluated for safety, and are not approved by the regulatory agency for use by patients. However, there is need for testing and monitoring of these herbal products due to the burden of unauthorised advertisement with unsubstantiated claims of cure of serious diseases with the intention of deceiving members of the public.

NAFDAC has initiated the evaluation of some herbal medicines, especially those claimed to cure HIV/AIDS amongst others [172]. The regulatory Agency has also established guidelines for registration and listing of herbal medicines and related products to be followed by manufacturers, in order to control them [173]. In this way, herbal medicine preparations would be monitored for safety in Nigeria, as presently implemented in other countries such as Thailand, where intensive monitoring for specific herbal products is in place [174].

3.1.6 Pharmacovigilance in Nigeria

The National Pharmacovigilance Centre (NPC) was established in 2004 within NAFDAC, and became a member of the WHO Programme for International Drug Monitoring the same year.

The NPC is composed of a pharmacovigilance (PV) unit and Food and Drug Information Centre (FDIC). It is responsible for promoting rational and safe use of medicines through monitoring medicine safety and providing information to the public. The NPC organises workshops/trainings for healthcare professionals and consumers, and encourages them to report ADRs. Guidelines to help healthcare professionals and yellow forms for reporting ADRs are also distributed during these training sessions.

The NPC started receiving ADR reports in 2005. ADR reporting centres have also been established in all the geo-political zones of the country. These centres receive reports from hospital pharmacovigilance units and individuals, and forward them to the NPC headquarters where they are entered into the national ADR database. However, the NPC also receive reports directly from healthcare professionals and patients/consumers [19], and collaborates with the Uppsala Monitoring Centre (UMC) in Sweden where ADR reports are sent at regular intervals.

Since its establishment, ADR monitoring of post-marketing pharmaceutical products has continued, and has become a useful tool for the detection of signals to protect the public from hazards of drugs. In Nigeria, metamizole (dipyrone) was reported to account for 93% of analgesic drug prescriptions administered intramuscularly and also the preferred analgesic drug in trauma [175]. The intramuscular administration of this drug for its antipyretic and

analgesic properties resulted in several fatal reports of toxic epidermal necrolysis (TEN), and the outcome of its monitoring report by NAFDAC led to its withdrawal from the Nigerian market in 2005 [176, 177].

3.1.7 Awareness of ADR reporting

For pharmacovigilance to be relevant, it is important that a good system of reporting ADRs is put in place. The process of reporting ADRs is still in its infancy in Nigeria, and healthcare professionals are not fully aware of its importance and their responsibilities in this role. Evidence from what can be considered as a pilot study at a university hospital in Nigeria suggests the potential value of a pharmacovigilance unit [119]. The availability of reporting materials and adequate education of healthcare professionals on reporting procedures were identified as vital for a successful pharmacovigilance unit [119]. Although patients in Nigeria can have a role in reporting ADRs through community pharmacies as contact points, recent evidence suggests such facilities may not offer a reliable service [178, 179].

Lack of knowledge in pharmacovigilance is widespread among healthcare professionals in Nigeria [70, 119, 179-181]. However, there is good progress, for example, research suggests resident doctors in Nigeria are willing to improve their knowledge of ADR and pharmacovigilance [182]. Further research by way of nationwide survey may help inform on the scope and scale of the problem and also guide steps for facilitating improvements.

3.1.8 ADR Studies

Very few studies on the incidence of ADRs have been carried out in Nigeria. One of these was a combined retrospective and prospective study of patients admitted for various medical problems to a university hospital in Nigeria, which identified ADRs as a significant source of medical problems [183]. In using suspected ADRs observed in hospital records, the multidisciplinary team of researchers conducted a prospective study to assess those that were actually ADRs. They reported skin reactions as the most frequent ADRs. The other study of note was conducted by WHO in conjunction with the Nigerian regulatory agency for the monitoring of artemisinin combination therapy (ACT) drug in all the regions of Nigeria [184, 185].

Other ADR studies in Nigeria were specific for drugs such as antimalarials [186], and antiretrovirals [187, 188]. There is very limited information available on ADRs in Nigeria. This problem is compounded by the presence of a large number of substandard, counterfeit, contaminated medicines [189] and herbal products [170], which form part of the reports received by the NPC.

Analysis of the ADRs in the database will be conducted for the adult and child populations separately. It is hoped that the findings of this study will provide information on the toxicity of medicines used in Nigeria for adults and children.

3.2 METHODS

This study was designed to describe the ADR reports for adults aged 18 years and above, submitted to UMC by the Nigerian National Pharmacovigilance Centre from when it began receiving the reports in 2005 to December 2012.

3.2.1 Aim

To conduct descriptive analyses of ADR reports for Nigerian adults (18 years and above) in the database of the national pharmacovigilance centre in Nigeria.

3.2.2 Objectives

The main objectives of this research were to evaluate:

- Types of reports by year, and age and sex of patients
- Notifiers of ADRs
- Type of ADRs
- Type of drugs reported
- ADR outcome and severity
- Causality assessment of reports
- Drug related deaths

3.2.3 ADR data collection

Adverse drug reactions are reported using the yellow form provided by NAFDAC (see Appendix 1).

The ADR yellow form has provisions for details of:

- Patient's details (full name or initials, patient record number, age/date of birth, sex, weight, hospital/treatment centre)
- Adverse drug reaction (ADR) (description, date reaction started, date reaction stopped, was patient admitted due to ADR, outcome of reaction)
- Suspected drug including biologicals, traditional/herbal medicines and cosmetics, drug details (brand name, generic name, batch number, NAFDAC number, expiry date, name and address of manufacturer), indication for use, dosage, route of administration, date started, date stopped
- Concomitant medicines (brand or generic name, dosage, route, date started, date stopped, reason for use)
- Source of report (name of reporter, address, profession, signature, date, telephone number / e-mail).

The yellow form also includes a piece of advice to reporters. These forms are distributed to all hospital pharmacovigilance units and committees in all the 36 States, and PV centres situated in the six geopolitical zones of the country. ADR reports are received by the NPC from doctors, pharmacists, and other health professionals, who also assess the seriousness of the ADRs. Reports are also received from consumers, and pharmaceutical

companies are required to send ADR reports they have received for their products.

3.2.4 Transmission of reports

Reporters of ADRs complete the yellow form and send them to the local PV offices from where they are forwarded to the national centre [53]. The NPC also receive reports of ADRs directly from reporters via email, dedicated telephone line and mobile phone text message [190].

3.2.5 Report processing

Reports of suspected ADRs were received by the National Pharmacovigilance Centre in Nigeria from pharmacovigilance units in medical institutions and zonal pharmacovigilance centres located in all six geopolitical zones of the country. The individual reports contain age and sex of the patients and details of the reporter, ADR(s), and suspected and concomitant drug(s). Pharmacovigilance personnel review the reports for completeness of required information. Reports with incomplete information are followed up with the reporters for completion, as required by the WHO International Drug Monitoring Programme.

Causality assessments were made by the National Drug Safety Advisory Committee according to the WHO criteria [191]. The National Drug Safety Advisory Committee in Nigeria is made up of experts in pharmacovigilance. The ADRs were coded based on WHO Adverse Reaction Terminology (WHO-ART), and drugs were based on WHO Drug Dictionary Enhanced

(WHO-DD) [192]. Serious ADRs were defined as those resulting in death, life-threatening, required/prolonged hospitalisation, and significant disability /incapacity or congenital anomaly/birth defect [193].

All the reports meeting the minimum requirements of reporter and patient details, suspect drug information, ADR seriousness and outcome, and drug causality assessment were entered into the national ADR database. They are then forwarded to the UMC who receive anonymised reports from over 117 countries, which are then entered in the WHO Global Individual Case Safety database, VigiBase. The assessments of ADRs to determine whether they were critical were performed at the WHO-UMC. WHO-ART critical terms are those which may be indicative of a serious disease state, and need more decisive action than other ADRs [194]. All the reports entered into VigiBase until December 2012 were obtained and described according to reporters, ADRs in WHO-ART preferred terms and system organ classification [13]. The frequencies of suspect drugs were described in WHO-DD preferred base name. Patients whose ages were between 18 years and above were considered adults and reports which had more than one drug were considered separately for each drug.

3.2.6 Approval for use of data

An application for use of the ADR data was made to the authorities of the regulatory agency (see Appendix 2), and an approval was secured (see Appendix 3). The approval was subsequently submitted to WHO International Adverse Drug Reaction Monitoring Centre, Uppsala, in Sweden for access to the data.

3.2.7 Data extraction

Data on ADRs received for Nigeria from 2005 to December 2012 was obtained from the Uppsala Monitoring Centre VigiBase, and included reports for adults and children. The extracted information included notifiers of ADRs, age and sex of patients, ADRs in reported and preferred terms, seriousness and outcome of ADRs, suspect drugs and indication for use, and causality assessments. The data elements extracted for each report are as shown in Appendix 7.

3.2.8 Analytical procedure

The reports were categorised into year of submission, age and sex of patients, and type of notifier. ADRs were described according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) [195], preferred and WHO-ART critical terms. Seriousness of ADRs were categorised into life threatening, caused/prolonged hospitalisation, disabling/incapacitating, other significant and death [193]. The drugs were grouped into classes. Causality assessment was described according to WHO criteria [9] – certain, probable, possible and unlikely. The outcomes of the ADRs were also analysed.

3.3 RESULTS

3.3.1 Reports by year, sex and age group

During the 8-year period, 4783 reports in 4783 patients were submitted to UMC. The average reporting rate was 7.2 reports per million individuals per

year, based on the population estimate of 2012. The number of reports ranged from 22 to 103 for each year between 2005 and 2009, thereafter, the number increased from 273 in 2010 to 3001 in 2012 (Figure 3.1).

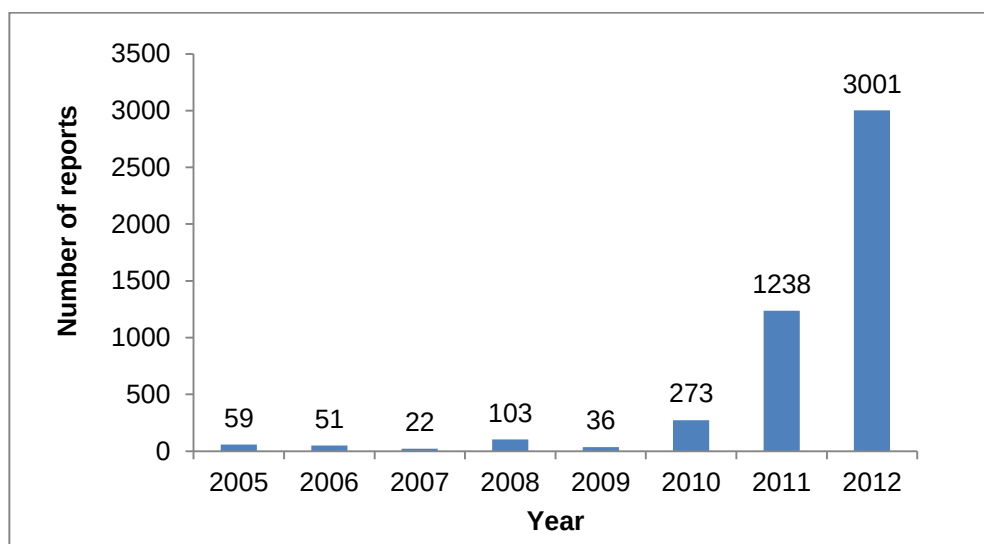


Figure 3. 1: Number of reports by year

Two-thirds of the reports involved women (3145, 68%) in the cases where gender was indicated (4650, 97%). There were few reports for elderly adults (Table 3.2).

Table 3.2: Number of reports by age

Age group	Reports (n)	%
18 – 29 years	1216	25
30 – 39 years	1560	33
40 – 49 years	1034	22
50 – 59 years	449	9
≥ 60 years	251	5
Unspecified	273	6
Total	4783	100

3.3.2 Reporters of ADRs

Pharmacists submitted the majority (3799, 79%) of reports (Figure 3.2).

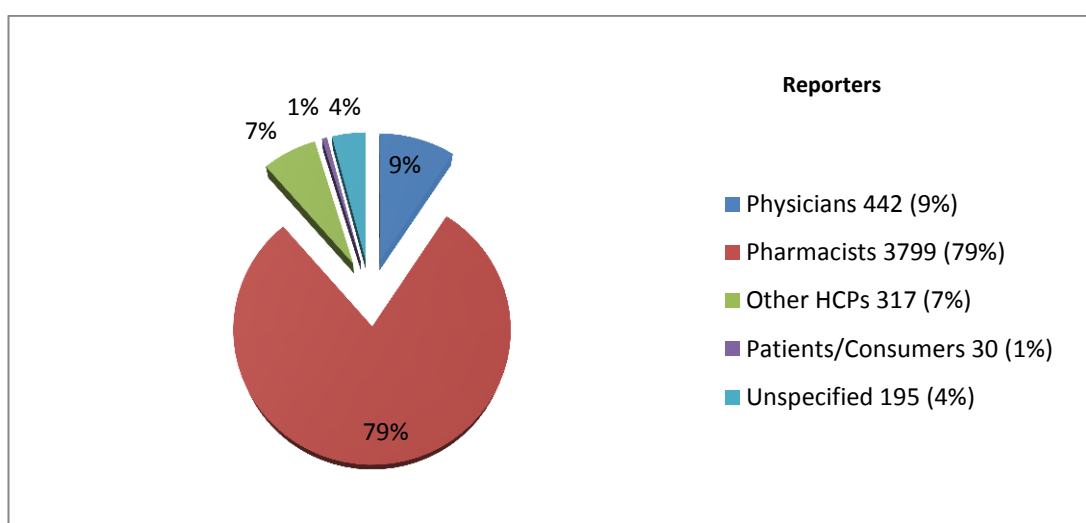


Figure 3. 2: Notifiers and proportion of reports

The number of reports from pharmacists has increased over the years (Figure 3.3). The majority of the reports in 2007 were from physicians, thereafter, the number progressively decreased to 7% in 2012. No reports were received from pharmaceutical manufacturers.

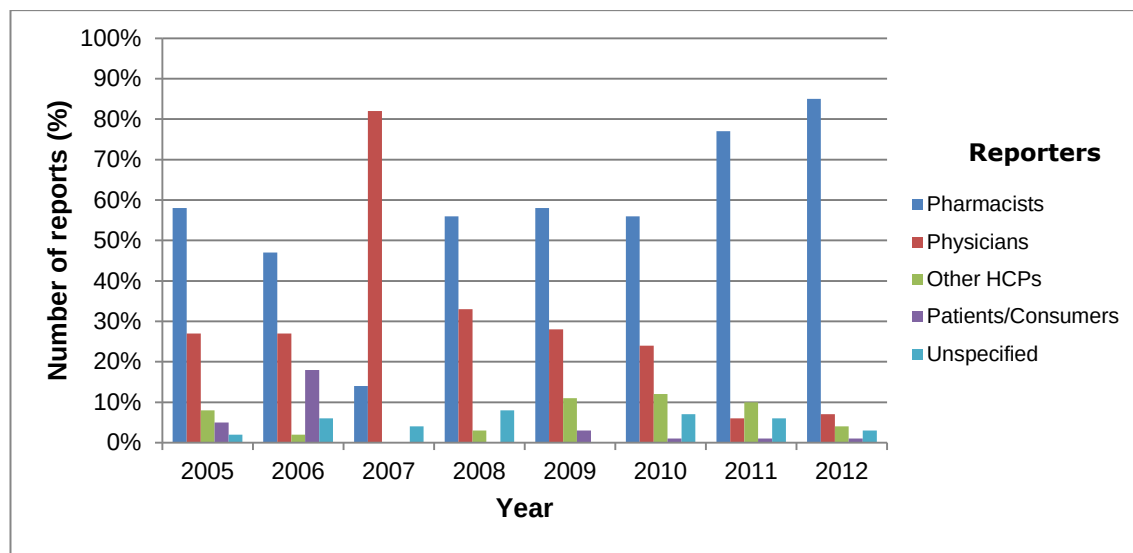


Figure 3. 3: Notifiers of reporters by year

3.3.3 Adverse drug reactions in system organ class

Almost 1 in 4 suspected ADRs involved the skin. Disorders of the gastrointestinal system and nervous system were the other systems most frequently affected (Figure 3.4).

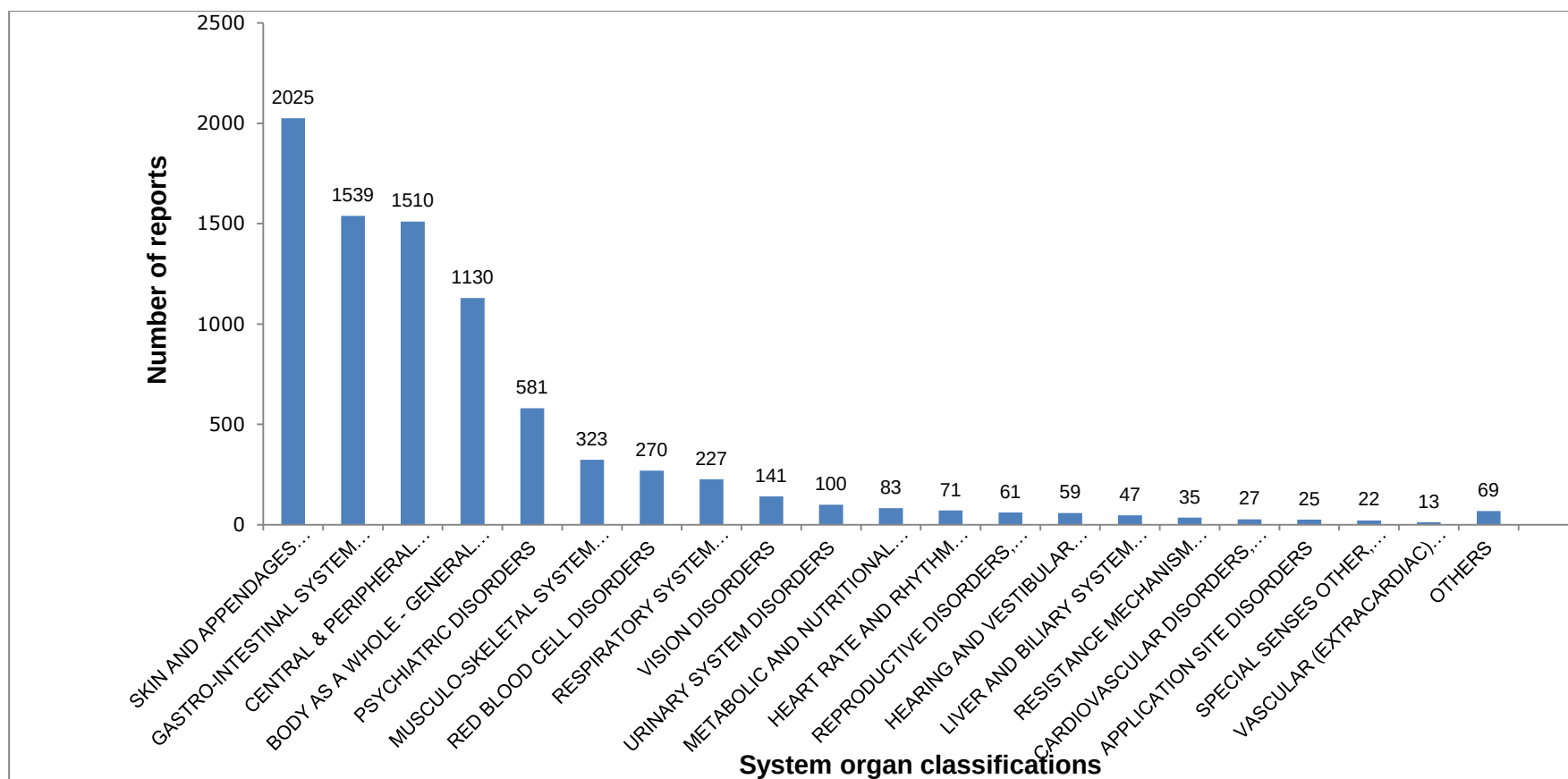


Figure 3. 4: Distribution of ADRs in system organ class

The most frequently reported individual reactions were rash, pruritus, headache, and dizziness (Table 3.3). Stevens Johnson syndrome was experienced by 164 patients.

Table 3. 3: 30 Most frequent reported ADRs (preferred terms)

ADRs	n	%
Rash	812	9.7
Pruritus	594	7.1
Headache	495	5.9
Dizziness	453	5.4
Vomiting	391	4.7
Nausea	322	3.8
Abdominal pain	317	3.8
Peripheral neuropathy	301	3.6
Anaemia	253	3.0
Asthenia	237	2.8
Fatigue	211	2.5
Diarrhoea	205	2.4
Stevens Johnson syndrome	164	2.0
Anorexia	164	2.0
Fever	156	1.9
Insomnia	154	1.8
Muscle weakness	125	1.5
Myalgia	107	1.3
Coughing	101	1.2
Malaise	94	1.1
Skin discolouration	88	1.0
Chest pain	74	1.0
Abnormal vision	68	0.8
Agitation	67	0.8
Maculo-papular rash	67	0.8
Arthralgia	64	0.8
Dyspnoea	64	0.8
Dyspepsia	62	0.7
Pain	61	0.7
Hypoaesthesia	59	0.7
Others	2028	24.3
Total	8358	100

3.3.4 Suspect drugs

A total of 6876 drugs in preferred base names were suspected. The most frequently reported class of drugs were antiretrovirals, antibiotics and antimalarials (Table 3.4). Antiretrovirals were responsible for over three quarters of the reports.

Table 3. 4: Drug Classes and number of times suspected

Drug class	n	%
Antiretrovirals	5264	76.6
Antibiotics	498	7.2
Antimalarials	426	6.2
Analgesics	133	2.0
Anti-inflammatory	127	1.8
ACE inhibitors	68	1.0
Blood products	42	0.6
Diuretics	39	0.6
Calcium channel blockers	34	0.5
Antidiabetics	29	0.4
Antineoplastics	21	0.3
Antiepileptics	19	0.3
Muscle relaxants	19	0.3
Vitamins	18	0.3
Antipsychotics	13	0.2
Antacids	13	0.2
Propulsives	10	0.1
Beta blocking agents	10	0.1
Others (less than 10)	93	1.3
Total	6876	100

The eleven most frequently reported individual drugs were all anti-infective agents (Table 3.5). Among the antiretrovirals, nevirapine, lamivudine and zidovudine were the most frequently suspected. The most frequently suspected antibiotics were cotrimoxazole and ciprofloxacin, and pyrimethamine/sulfadoxine and amodiaquine/artesunate were the most frequently suspected antimalarials.

Table 3. 5: Individual drugs and number of times suspected

Drugs	Number of times suspected (n)
Nevirapine	1508
Lamivudine	1063
Zidovudine	986
Zidovudine/nevirapine/lamivudine	362
Efavirenz	356
Stavudine	352
Cotrimoxazole	233
Tenofovir	215
Stavudine/nevirapine/lamivudine	121
Zidovudine/lamivudine	120
Pyrimethamine/sulfadoxine	80
Tramadol	71
Amodiaquine/artesunate	64
Artesunate	58
Emtricitabine	57
Diclofenac	48
Lisinopril	47
Artemether/lumefantrine	35
Ciprofloxacin	34
Emtricitabine/tenofovir disoproxil fumarate	33
Emtricitabine/tenofovir	33
Dapsone/chlorproguanil hydrochloride	32
Nifedipine	22
Chloroquine	20
Chlorproguanil	18
Metronidazole	18
Pefloxacin	18
Amoxicillin	17
Furosemide	17
Amodiaquine	16
Naproxen	16
Ceftriaxone	15
Dapsone	15
Ibuprofen	15
Mefloquine/artesunate	15
Metformin	15
Ritonavir/lopinavir	15
Carbamazepine	14
Paracetamol	14
Nimesulide	14
Stavudine/lamivudine	14
Dihydroartemisinin	13
Pentazocine	13
Levofloxacin	13
Clavulanate potassium/amoxicillin trihydrate	12
Iron	12
Metamizole	11
Amodiaquine hydrochloride/artesunate	11
Amlodipine	11
Isoniazid	11
Rifampicin	11

3.3.5 Outcome of ADRs

A total of 4783 adults experienced 8358 ADRs, representing 1.7 ADRs per report. There were 115 deaths, representing 2.4% of the reported population. At the time of reporting, 1642 patients had recovered from the reported ADRs, and 154 patients had not recovered (Table 3.6). The outcome of almost equal number of reports were not known or not specified.

Table 3. 6: ADR outcomes for all reports

Outcome	Reports (n)
Death	115
Not recovered	154
Recovered	1642
Recovered with sequelae	50
Recovering	355
Unknown	1386
Unspecified	1383

3.3.6 Severity of reports

A total of 184 reports were considered serious with an indication of level of severity. The proportions of serious reports with severity in each year are shown in Figure 3.5. A further 131 reports were considered serious without severity criterion.

The proportions of reported deaths in relation to other serious reports were higher for the years 2011 and 2012. Of the 98 deaths reported between 2011 and 2012, antiretrovirals were the reported drugs in 42 (43%) of the cases.

No death was reported in 2007. The proportion of reports with ADRs which caused/prolonged hospitalisation was more than reports with life threatening and disabling/incapacitating ADRs.

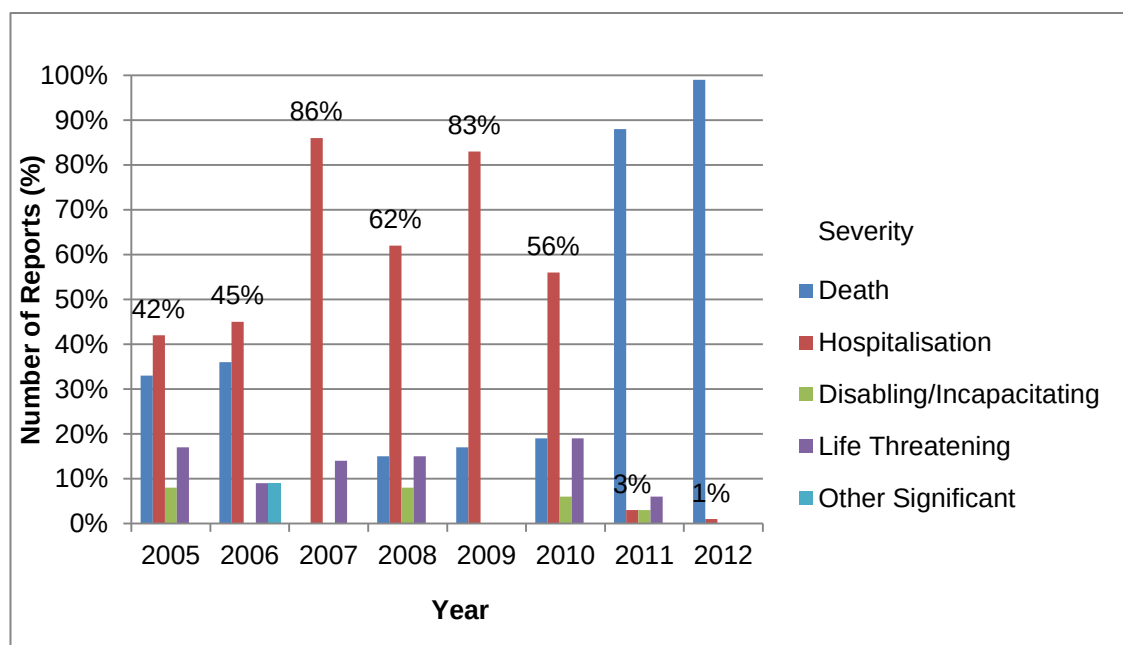


Figure 3. 5: Severity reports (184) by year

3.3.7 Causality assessment of reports

Of the total 315 reports considered as serious, 214 reports corresponding to 400 ADRs were assessed for causality (Table 3.7). The causality assessments for the reports with seriousness criteria were: probable 33, possible 140, unlikely 38, and unknown 3 reports. None of the serious ADRs were assessed as certainly related to a drug.

Table 3. 7: ADRs with seriousness criteria and causality assessments

Assessment	ADRs	
	n	%
Probable	38	9
Possible	299	75
Unlikely	60	15
Unknown	3	1
Total	400	100

3.3.8 Drug – related deaths

A total of 151 suspect drugs were associated with the 115 deaths reported in this study (Table 3.8). The reported deaths were made up of 73 (63%) females, and 39 (34%) males, and gender was not specified in 3 cases. Antiretrovirals, antibiotics, and antimalarials were suspected more than the other classes of drugs.

Table 3. 8: Classes of drugs associated with fatalities

Class of medicines	Number of times suspected (n)	%
Antiretrovirals	65	43.0
Antibiotics	26	17.2
Antimalarials	19	12.6
Cardiovascular agents	9	6.0
Antidiabetics	8	5.3
Anti-inflammatory	4	2.7
Antineoplastics	3	2.0
Analgesics	2	1.3
Psycholeptics	2	1.3
Antacids	2	1.3
Antithrombotics	2	1.3
Corticosteroids	2	1.3
Others	7	4.7
Total	151	100

For the individual drugs, nevirapine, zidovudine and cotrimoxazole were more frequently associated with the fatalities (Table 3.9). Three reports of death were associated with unknown drug products; phosphur dezin, herbal pollen extracts and zinc phosphide.

Table 3. 9: Fatalities and individual drugs

Drugs	Number of times suspected (n)	%
Nevirapine	21	13.9
Zidovudine	12	8.0
Cotrimoxazole	10	6.6
Lamivudine	9	6.0
Pyrimethamine/sulfadoxine	8	5.3
Zidovudine/nevirapine/lamivudine	5	3.3
Efavirenz	4	2.7
Glibenclamide	4	2.7
Metformin	4	2.7
Stavudine	3	2.0
Metronidazole	3	2.0
Tenofovir	3	2.0
Artesunate	2	1.3
Betamethasone	2	1.3
Furosemide	2	1.3
Letrozole	2	1.3
Lisinopril	2	1.3
Mefloquine/artesunate	2	1.3
Piroxicam	2	1.3
Rifampicin	2	1.3
Zidovudine/lamivudine	2	1.3
Others*	47	31.1
Total	151	100

**Other drugs associated with one fatality*

A total of 263 ADRs were associated with the 115 reported deaths (Table 3.10). Stevens Johnson syndrome, diarrhoea, dyspnoea and coma were the most frequently reported fatal ADRs. Cotrimoxazole and nevirapine were mostly associated with cutaneous reactions, and mostly antiretrovirals were implicated with diarrhoea. A total of 58 patients died from uncertain ADRs.

Table 3. 10: Deaths reported and suspected drugs

ADRs	Number of Patients	Drugs and number of times suspected
Stevens Johnson syndrome, epidermal necrolysis and skin exfoliation	21	Please See Table 3.11
Diarrhoea	8	Zidovudine/Nevirapine/Lamivudine (2), Ritonavir+Lopinavir (1), Lamivudine+Efavirenz+Tenofovir (1), Emtricitabine/Tenofovir (1), Nevirapine+Lamivudine+Stavudine (1), Atenolol (1), Diclofenac+piroxicam (1)
Dyspnoea	6	Ampicillin/Cloxacillin (1), Griseofulvin (1), Rifampicin (1), Ofloxacin (1), Zinc phosphide (1), Meglumine amidotrizoate (1)
Coma	4	Glibenclamide (2), Glibenclamide+metformine (1), Letrozole (1)
Anaphylactic reaction	2	Ampicillin/Cloxacillin (1), Metronidazole (1)
GIT Haemorrhage	2	Diclofenac (1), Piroxicam (1)
Renal failure	2	Emtricitabine/tenofovir disoproxil fumarate (1), Vancomycin (1)
Hypertension	2	Zidovudine/Nevirapine/Lamivudine (1), Mefloquine/artesunate (1)
Syncope	2	Mefloquine/artesunate (1), Letrozole (1)
Cerebral haemorrhage	1	Enoxaparin (1)
Haemolysis	1	Dapsone/chlorproguanil HCl (1)
Hepatocellular damage	1	Herbal pollen extracts (1)
Cardiac arrest	1	Metronidazole (1)
BP fluctuation	1	Ofloxacin (1)
Skin necrosis	1	Tetanus vaccine (1)
Arrhythmia	1	Chloramphenicol (1)
Tongue paralysis	1	Rabeprazole (1)
Uncertain*	58	Various drugs
Total	115	

*Cause of death uncertain

Table 3. 11: Fatal skin reactions and suspected drugs

Skins reactions	Number of Patients	Drugs and number of times suspected
Stevens Johnson syndrome	16	Pyrimethamine/sulfadoxine (4), Cotrimoxazole (3), Nevirapine (3), Cotrimoxazole+Nevirapine (2), Artesunate (1), Carbamazepine (1), Rifampicin (1), Clavulanate potassium/Amoxicillin trihydrate (1)
Toxic epidermal necrolysis	3	Pyrimethamine/sulfadoxine (1), Nevirapine (1), Metamizole (1)
Skin exfoliation	2	Allopurinol (1), Cotrimoxazole (1)
Total	21	

3.3.9 Critical ADRs

WHO-Adverse Reaction Terminology (WHO-ART) critical ADRs were also evaluated. WHO-ART critical ADRs are reported ADRs which may be indicative of serious disease states, and need quick and decisive action [194], and may or may be reported in the database as serious ADRs. These ADRs are classified by WHO-UMC (see Appendix 8). A total of 930 patients experienced a variety of WHO-ART critical ADRs (Table 3.12). These critical ADRs were not associated with the fatal ADRs in the database. The most frequently reported critical ADRs were peripheral neuropathy and Stevens Johnson syndrome. Even though these two ADRs were considered critical, only Stevens Johnson syndrome was seen to be associated with some fatal reports (Tables 3.10 and 3.11).

Table 3. 12: Critical ADRs

Critical terms	n	%
Peripheral neuropathy	298	30.6
Stevens Johnson syndrome	159	16.3
Mouth oedema	44	4.5
Face oedema	33	3.4
Angioedema	24	2.5
Skin exfoliation	22	2.3
Hallucination	21	2.2
Neuropathy	20	2.1
Polyuria	20	2.1
Hearing decreased	19	2.0
Epidermal necrolysis	14	1.4
Oedema generalised	14	1.4
Coma	12	1.2
Hyperpyrexia	12	1.2
Anorexia nervosa	11	1.1
Epistaxis	11	1.1
Immune system disorder	11	1.1
Others (10 or less)	228	23.5
Total	973	100

3.4 DISCUSSION

3.4.1 ADR reports by year and patients

Under-reporting is a general problem in pharmacovigilance [196, 197]. During the formative years of the NPC, the number of reports received ranged from 22 to 103, and dramatically increased from 273 in 2010 to 3001 in 2012. Following the directives from WHO, the Nigerian government in conjunction with non-governmental organisations instituted programmes to support and care for HIV/AIDS patients [198]. The increase in the number of reports in the last three years for this group of population, was due largely to encouragement of healthcare professionals who were involved in the programme by the sponsors, to report all ADRs experienced by HIV/AIDS patients following antiretroviral therapy [199]. Majority of the ADRs were reported for female patients. This may be due to the high number of female HIV/AIDS sufferers in Nigeria [188], female polypharmacy [200], and other unidentified sex-specific risk factors [201].

The elderly are known to be at a higher risk for developing ADRs due to age-related alterations in drug pharmacokinetics, co-morbidities, and greater risk of multiple drug exposures [202]. It is also believed that the elderly use more medicines than younger people because of aging, and are expected to experience more ADRs. The analysis showed that ADR reports for people above 60 years old were fewer than those reported for younger adults. This is similar to other reports from low income countries [87, 101]. This may be attributed to the high number of reports on antiretroviral drugs, the majority of which were for younger adults aged between 30 and 39 years old. In Nigeria,

under-reporting is largely due to lack of knowledge in pharmacovigilance among healthcare professionals [70, 179, 181], and this can be improved upon by education [119], an approach which has been adopted successfully in Cuba [113].

3.4.2 Notifiers of ADRs

The Act establishing the national pharmacovigilance centre does not make it mandatory for pharmaceutical manufacturers in Nigeria to send ADR reports on their products to the regulatory agency, as is required by FDA in United States [49]. Consequently, ADR reports were not received from pharmaceutical manufacturers in this study. This observation differed from the study conducted in the Czech Republic ADR database where one third of the reports were provided by marketing authorisation holders [83]. In high income countries where pharmacovigilance is developed, it is mandatory for drug manufacturers to submit ADR reports to the regulatory authorities of countries where their products are approved for public use. The marketing authorisation holders receive these reports from healthcare professionals and process them according to established ICH guidelines before submitting to the regulatory authorities [203].

The result of this study revealed that ADR reports were only received from physicians, pharmacists and other healthcare professionals including nurses, and consumers/patients. The number of reports submitted by pharmacists was more than the reports from physicians, other healthcare professionals and patients combined. This may be attributed to the involvement of pharmacists with the HIV/AIDS programme in Nigeria, who were instructed to

report all reactions associated with antiretroviral therapy. Antiretroviral reports formed more than 70% of the cases. This observation differed from the findings in the studies reviewed, where physicians submitted most of the reports. In particular, it differed from the results of study conducted in the Ethiopian ADR database between 2002 and 2007, where physicians also reported more ADRs than the other healthcare professionals [101]. Patients have direct access to pharmacists in Nigeria, and inform them of ADRs they experience following drug use. This may be a contributory factor to the higher number of ADR reports submitted by pharmacists to the NPC.

Patients reported the least number of ADRs in this study as opposed to the very high number of reports they send in Denmark, The Netherlands and UK [82, 93, 204]. However, in order to encourage patients and the public to report ADRs, the National Pharmacovigilance Centre in Nigeria has provided a dedicated toll-free telephone line for reporting ADRs experienced by patients [190]. This method has been reported to facilitate pharmacovigilance and follow up of reported ADRs [205]. A practical way of encouraging ADR reporting by healthcare professionals may be to provide incentives such as pens with a reminder logo which had been shown to improve participation in monitoring of ADRs [206].

3.4.3 Adverse drug reactions

Rash and pruritus were the most frequent ADRs reported in Nigeria. This observation was consistent with my systematic review in Chapter 2 and the only previous study in Africa (Ethiopia) [52, 99, 101], and differed from

studies conducted in UK and The Netherlands [82, 93], where nausea and myalgia were the most frequently reported ADRs respectively.

3.4.4 Seriousness of ADRs

The proportion of serious ADR reports observed (6.7%) was lower than in the studies reviewed in Chapter 2, from Asia (16 – 24%) and Europe (8 – 74%). However, the proportion of reported deaths (2.4%) was similar to that reported in Korea (2.4%) [51] and Europe (0.6 – 3.8%). The data information was not complete for all the reports in the Nigerian ADR database. For the reports that had complete information on reporters and ADR category of serious and non-serious in this study compared to those reported in Denmark [58], the proportion of reported serious ADRs was similar for physicians (49% v 45%), and varied for consumers (78% v 46%). The difference in the proportions observed may be attributed to the duration of studies and what the reporters consider of the ADRs based on knowledge of the reactions and reporting experience.

3.4.5 ADRs and causality assessment

Causality assessment is the evaluation of the likelihood that a particular treatment is the cause of an observed adverse event. Drug causality assessment for ADRs is always a complicated process in pharmacovigilance, especially in patients with polypharmacy and long-term use of drugs, and the impossibility of dechallenging and rechallenging of patients with suspect drugs. However, in fatal cases with prolonged disease, clinicians are more likely to attribute cause of death to underlying diseases rather than to

therapeutic drugs. Causality assessments for the ADRs in the database were performed using the WHO criteria [191], and other studies [52, 99] have used the Naranjo's ADR probability scale. The majority of the ADRs were assessed as 'possible' 71%, probable 9%, and none was assessed as 'certain'. These findings were not consistent with the causality assessment observed in the Asian studies reviewed in which ADRs assessed as 'possible' ranged from 32-44% [51, 52, 99]. Factors which could contribute to differences in causality assessment may include the individual patient medical conditions, response to drugs, and dechallenge and rechallenge outcome of the ADRs. Due to differences in drug use and types, and other medical conditions for which they were prescribed in addition to drug-drug interactions, it may not be easy to assess causality, and even compare between studies.

3.4.6 Drugs

The ADR database contained only information on reports of ADRs, and it was not possible to compare drug use in the population with reported drugs. Nevirapine, lamivudine and zidovudine were the individual drugs mostly reported. They were mostly associated with skin reactions which were expected ADRs that had already been recognised for these drugs. This observation was consistent with the global patterns of ADRs, especially for African countries, where skin and subcutaneous tissue disorders were reported to be associated with antiretroviral drugs [101]. However, it differed with the other studies reviewed where nervous system drugs [58, 87, 96] were most commonly reported.

HIV is a major clinical problem in Africa. The Ethiopian government made available antiretroviral drugs to support patients with HIV/AIDS through the President's Emergency Plan for AIDS Relief (PEPFAR) in view of the prevalence rate of the disease [207]. Nigeria has the second highest number of HIV infections reported globally each year, and 240,000 people died from HIV/AIDS in 2012 [129]. The Government in partnership with non-governmental organisations [199, 208] provided antiretroviral drugs for the early treatment of HIV/AIDS. In all these programmes, the sponsors encouraged healthcare professionals to report therapy related ADRs to the national pharmacovigilance centres of the respective countries. This may have attributed to the high number of antiretroviral related ADRs in this study.

3.4.7 Drug – related deaths

Anti-infective agents were the group of drugs responsible for the most fatal ADRs in this study, with antiretrovirals accounting for more than a third of the total drugs suspected. This could be attributed to the large number of HIV/AIDS sufferers in Nigeria, as it is presently ranked second highest in the number of new infections reported globally each year [129].

Antibiotics and antimalarials were the next classes of drugs most frequently associated with fatalities. The indiscriminate use of antibiotics and antimalarials for self-medication [209] by patients may be associated with the high number of times they were suspected with the fatal reports in this study. Other classes of drugs were associated with higher number of fatalities in other related studies. Antibiotics in Italy [92], anticoagulants in Sweden [95], and nervous system drugs followed by anti-infectives, musculoskeletal and

cardiovascular system agents in Canada [210], were most frequently associated with fatal ADRs.

About 80 per cent of the reports in this study belong to young adults aged 18 to 49 years, who also had the highest proportion of fatal ADRs. They were mostly HIV/AIDS sufferers who had been on antiretroviral drug therapy.

The finding in this study differs from previous studies on drug-related mortality [92, 95], where elderly people in Sweden and Italy experienced more fatal ADRs as a result of changes in pharmacokinetics and pharmacodynamics, polypharmacy and drug interactions which are known risk factors for ADRs.

There was no dominance of a particular drug associated with the fatal ADRs reported in this study. The fatal skin reactions reported were all known to be associated with the drugs implicated. Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare severe cutaneous adverse reactions related to a variety of medications. They have a significant public health impact because of high mortality and morbidity. The incidence of SJS and TEN is low; however, the mortality rate has been estimated at 5% for SJS and 30-50% for TEN [211].

Pyrimethamine/sulfadoxine, cotrimoxazole and nevirapine were the drugs mostly associated with fatal cutaneous reactions in this study (see Table 11). Cotrimoxazole was previously found to be the most common drug responsible for Stevens Johnson syndrome [212], and among HIV patients, nevirapine followed by cotrimoxazole are mostly implicated [213]. Nevirapine was approved by United States – Food and Drug Administration (US-FDA) for the treatment of HIV infection. Its active metabolites do not go through

phosphorylation when used as a part of combination therapy, and consequently, plasma HIV viral load suppression occurs very quickly [214]. Cotrimoxazole is commonly used with nevirapine for the treatment and prophylaxis of *Pneumocystis jiroveci* pneumonia and several bacterial infections in HIV positive people, and Stevens Johnson syndrome and other fatal cutaneous reactions have been associated with them [215].

Nevirapine alone has been associated with Stevens Johnson syndrome or epidermal necrolysis in clinical trials, but its benefits outweigh these risks [216]. It is not possible to link Stevens Johnson syndrome and nevirapine with certainty as there are no in-vitro or in-vivo diagnostic tools to confirm their association. In this study, nine fatalities resulting from Stevens Johnson syndrome and epidermal necrolysis were 'possibly' related to cotrimoxazole, nevirapine, and cotrimoxazole/nevirapine respectively, according to WHO-UMC causality assessment criteria [191].

Pyrimethamine/sulfadoxine is used as treatment and chemoprophylaxis of chloroquine-resistant *Falciparum* malaria in Nigeria [217]. Since 1982, the fixed combination of pyrimethamine and sulfadoxine has been used for malaria prophylaxis, especially by travellers at risk of acquiring the chloroquine-resistant *Plasmodium falciparum*. Severe cutaneous reactions have been linked with pyrimethamine/sulfadoxine.

Allopurinol and carbamazepine have been reported as the most common single causative drugs causing severe cutaneous adverse reactions in an analysis of the Korean ADR database [218]. Allopurinol is a xanthine oxidase inhibitor, which blocks uric acid formation, and is utilised as prophylaxis in patients with an elevated risk of hyperuricaemia and tumour lysis syndrome.

It has been demonstrated to cause variable skin toxicities, some of which have progressed to severe, life-threatening, and fatal toxicity [219]. Allopurinol has been reported as the most common cause of SJS and TEN in Europe and Israel [220]. The pathogenesis of allopurinol-induced SJS and TEN is consistent with a delayed-type immune-mediated reaction [221], and human leucocyte antigen, HLA-B*5801 allele has been associated with increased risk of developing SJS/TEN in patients treated with allopurinol [222]. It is not known if the patient who died in this study was predisposed to allopurinol-induced SJS/TEN; however, a potential genetic-based immunological marker such as HLA-B*5801 has been suggested as a screening test for patients being treated with allopurinol [222]. This is useful to prevent cases of severe cutaneous reactions in patients treated for hyperuricaemia and tumour lysis syndrome.

Rifampicin or the combination with isoniazid is used for the treatment of tuberculosis. There is limited information for rifampicin associated Stevens Johnson syndrome in the literature for adults; however, this link has been observed and led to the death of HIV patients in Togo, West Africa [223].

3.5 CONCLUSION

The findings of this study revealed that majority of ADRs in Nigeria were associated with antiretroviral drugs, and these were reported mainly by pharmacists. Nearly two-thirds of the reports were received in 2012, mostly for antiretroviral agents. This was due to instructions given to coordinators of the HIV/AIDS programme to report all reactions associated with antiretroviral therapy. Reactions belonging to skin and appendages disorders were most

frequently reported in line with findings in the studies reviewed. Serious ADRs accounted for 6.5% of the total ADRs, and death, mostly from Stevens Johnson syndrome, was the outcome for 115 out of the 4783 notifications. The high number of reports received for antiretroviral drugs within the two years shows pharmacovigilance for other classes of drugs such as antimalarials could also be implemented successfully in Nigeria if given the same approach. A major limitation of the study was data incompleteness which made the interpretation of the reports difficult.

CHAPTER FOUR

ADVERSE DRUG REACTIONS IN NIGERIAN CHILDREN

4.1 INTRODUCTION

In the previous chapter, I described ADRs in adults in Nigeria. In this chapter, I will focus on Nigerian children. Nigeria is the most heavily populated country in Africa, and children under the age of 18 years constitute 85 million of the population based on the estimate of 2012 [86]. It has a high mortality rate for children under five years old (124 per 1000 live births). According to WHO [224], the main causes of death in children under 5 years in 2013 were malaria, other infections, prematurity, birth asphyxia and birth trauma (Table 4.1).

Table 4. 1: Major causes of death in children under 5 years [224]

Causes of death	Percentage (%)
Malaria	21
Other causes	16
Acute lower respiratory infections	15
Prematurity	12
Birth asphyxia	10
Diarrhoea	10
Neonatal sepsis	5
Injuries	5
Congenital anomalies	3
HIV/AIDS	3
Measles	1

The Ministry of Health, in collaboration with WHO, have launched programmes to prevent and reduce child mortality arising from malaria [225, 226] and diarrhoeal diseases [227], alongside the expanded programme on immunisation [228]. The aim of the immunisation programme is to protect children against tuberculosis, pertussis, polio, measles, diphtheria and tetanus. Oral rehydration therapy is also made available to rehydrate a dehydrated child caused by diarrhoea.

These programmes have not produced the desired result of reducing child mortality in Nigeria. This may partially be due to the quality of drugs used in managing these conditions. Most of the medicines used in Nigeria are imported from abroad, and only a few are produced in the country without adequate quality control measures. Research has shown that antimalarials used for treating malaria in Nigeria can be of low quality [229, 230], and antimalarial syrups used for children were found to be substandard [231]. Counterfeit anti-infective agents used for treating various forms of infections also flood the medicine supply chain in Nigeria. These drugs are found to have lowered efficacy [232] and resistance to these products have been reported in Nigeria [233].

The vast majority of ADRs are unreported and the true incidence of ADRs is unknown [196]. Most previous reports of national pharmacovigilance programmes and ADRs in children have involved either high income countries [37, 79, 107], or countries with a high human development index such as Cuba [50, 113]. The review in Chapter 2 showed that ADR reporting rate is higher in Cuba compared with USA and countries in Europe. In Cuba, at least one in every 500 children experiences an ADR. The higher rate

observed in Cuba followed educational intervention regarding the reporting of ADRs by healthcare professionals [113].

A single centre study in Nigeria has reported ADRs in children from January 2004 to December 2006 [183]. However, this single centre study only identified 44 ADRs. The child reports in VigiBase for Nigeria have not been analysed since it started receiving ADR reports in 2005, and information on ADRs for children from this source is limited in the literature. Having described ADRs of Nigerian adults in the previous chapter, this chapter focuses on describing the ADR reports of children since the establishment of the National Pharmacovigilance Centre.

4.1.1 Aim

To conduct descriptive analyses of ADR reports in the database of the national pharmacovigilance centre in Nigeria, with a view of understanding the toxicity profiles of drugs in Nigerian children.

4.1.2 Objectives

The main objectives of this research will be to:

- Determine the number of ADR reports received per year
- Identify types of ADRs and drugs reported
- Identify ADR severity and outcome of reactions as reported
- Identify reports of death and drugs implicated
- Determine if causality assessments of drugs are reported
- Identify the most reported drug class for this population

4.2 METHODS

The processes of ADR data collection, transmission of reports, report processing, approval for use of the data, data extraction, and method of analysis has previously been described in Chapter 3. The age groups of children were divided into neonates (0 – 27 days), infants (28 days to 23 months), children (2 – 11 years) and adolescents (12 – 17 years) according to the International Conference for Harmonisation (ICH) guidelines on Clinical Investigation of Medicinal Products in the Paediatric Population [234].

4.3 RESULTS

4.3.1 Number of reports

The overall total number of reports received during the 8-year period was 5080, out of which 297 were for children aged 0 – 17 years. The average ADR reporting rate was 0.4 reports per million children per year, based on the 2012 population estimate of 85 million for this group of children. The highest number of reports, 182 (61%) were received in 2012 (Figure 4.1).

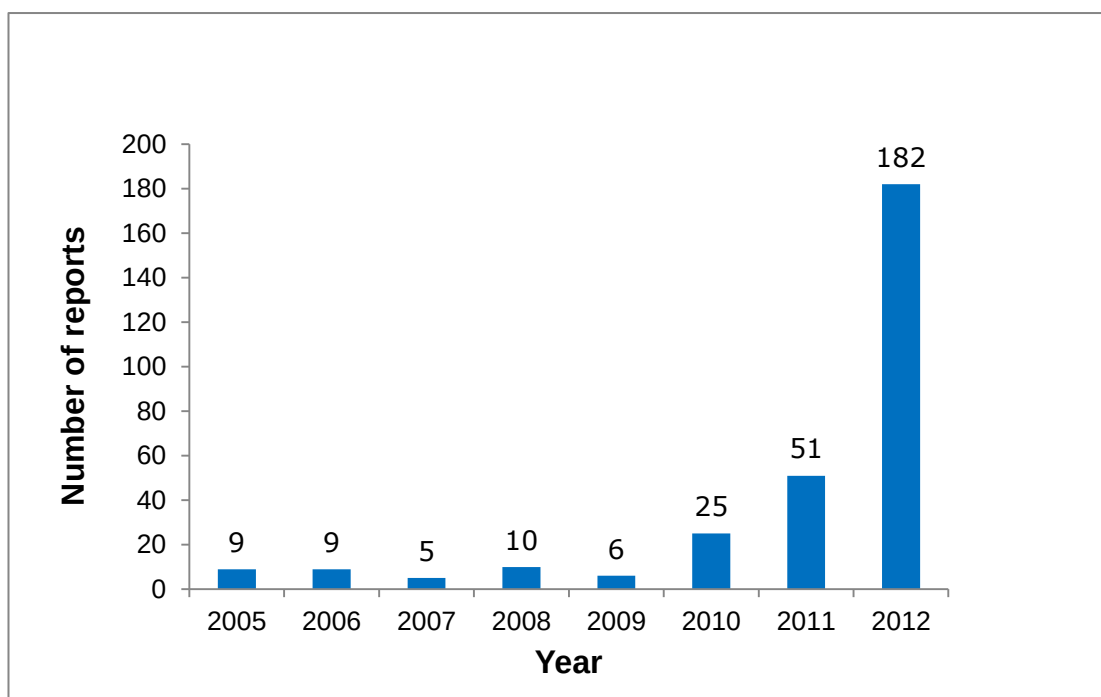


Figure 4. 1: Number of reports by year

4.3.2 Age group and sex

The distribution of reports according to age groups is as shown in Figure 4.2. The reports for children aged between 2 – 11 years were more than half of the total reports, 168 (57%), neonates had only 12 (1%) of the reports. In the cases where sex was reported, 56% were males. The proportion of males in each group was 33% for neonates, 53% for infants, 59% for children, and in adolescents, the proportion was 52%. Sex was not specified for a total number of 19 (5%) reports.

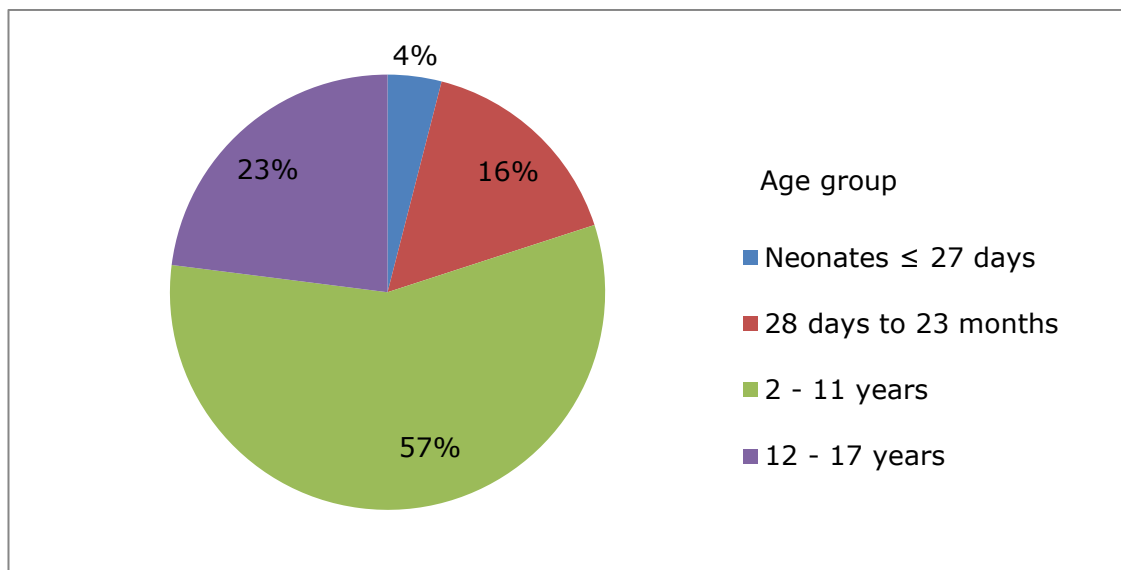


Figure 4. 2: Age distribution of reports

4.3.3 Type of reporters

Almost the same number of reports, 66 (22%) and 68 (23%) were received from physicians and other healthcare professionals (nurses, etc) respectively. Pharmacists reports were 147 (50%) of the total, and reporter type were not specified for 13 (4%) of the reports (Table 4.2). Other healthcare professionals reported more serious ADRs than physicians and pharmacists, and reporter types were not specified for more than 3% of the serious ADRs.

Table 4. 2: Reporter type, number of reports and serious ADRs

Reporter type	Reports		Serious ADRs	
	n	%	n	%
Physicians	66	22	15	25
Pharmacists	147	50	20	33.3
Other HCPs	68	23	23	38.3
Consumers	3	1	0	0
Unspecified	13	4	2	3.3
Total	297	100	60	100

4.3.4 Reported ADRs

The ADRs described according to system organ classification (SOC) and age groups are as shown in Table 4.3. ADRs belonging to skin and appendages disorders, general disorders and gastrointestinal system disorder were most frequently reported.

Table 4. 3: Distribution of ADRs (SOC) and age groups

Age group/SOC	Neonates ≤ 27 days	28 days to 23 months	2 – 11 years	12 – 17 years	ADR Total	
					n	%
Skin and appendages disorders	3	20	77	37	137	29.0
Body as a whole - general disorders	1	10	66	17	94	19.9
Gastro-intestinal system disorders	1	13	29	20	63	13.3
Central & peripheral nervous system disorders	0	4	25	12	41	8.7
Urinary system disorders	5	9	8	4	26	5.5
Psychiatric disorders	0	5	10	8	23	4.9
Respiratory system disorders	3	5	10	1	19	4.0
Musculo-skeletal system disorders	0	0	10	5	15	3.2
Red blood cell disorders	0	1	6	3	10	2.1
Vision disorders	0	2	6	1	9	1.9
Liver and biliary system disorders	0	0	6	1	7	1.5
Secondary terms – events	1	2	1	3	7	1.5
Application site disorders	0	0	1	5	6	1.3
Platelet, bleeding & clotting disorders	0	4	1	0	5	1.0
Metabolic & nutritional disorders	0	1	3	0	4	0.8
Hearing and vestibular disorders	0	0	2	0	2	0.4
Cardiovascular disorders – general	0	0	1	0	1	0.2
Heart rate and rhythm disorders	0	0	1	0	1	0.2
Reproductive disorders, Female	0	0	0	1	1	0.2
Resistance mechanism disorders	0	0	0	1	1	0.2
White cell and RES disorders	0	0	1	0	1	0.2
Total	14	76	264	119	473	100
ADR (% for age groups)	3	16	56	25	100	

The proportion of ADRs in each child sub-group was as follows: neonates 3%, infants 16%, children 56% and adolescents 25%.

The ADRs reported in preferred terms are shown in Table 4.4. A total of 473 ADRs were reported for the 297 cases, with an average of 1.6 ADR per report. The most frequently reported ADRs were rash, fever, pruritus and vomiting. There was no dominance for each of the other ADRs reported.

Table 4. 4: Most frequently reported ADRs (WHO-ART preferred terms)

ADR (preferred terms)	n	%
Rash	72	16
Fever	49	10
Pruritus	32	7
Vomiting	18	4
Diarrhoea	16	3
Asthenia	14	3
Stevens Johnson syndrome	14	2
Coughing	11	2
Headache	10	2
Abdominal pain	9	2
Anuria	8	2
Convulsions	8	2
Rigors	8	2
Jaundice	7	2
Others*	197	42
Total	473	100

* ADRs with 6 or less reports were grouped together as others

4.3.5 WHO-ART critical ADRs

A total of 73 children experienced a variety of reactions assessed by UMC as WHO-ART critical ADRs (Table 4.5). These ADRs were not assessed as serious in the reports. Stevens Johnson syndrome was experienced by 11 patients, and the suspect drug for 6 of these patients was nevirapine. Haemolysis was experienced by 5 patients following dapson/chlorproguanil.

Table 4. 5: WHO-ART Critical ADRs and suspect drugs

Critical ADRs	Number	Suspect drugs
Stevens Johnson syndrome	11	Nevirapine (6), Carbamazepine (1), Cloxacillin (1), Metamizole (1), Cotrimoxazole (1), Phenytoin (1)
Anuria	5	Calcium phosphate/coffee arabica/matricaria recutita/atropa belladonna (herbal teething mixture) (5)
Anaphylactic shock/reaction	5	Methotrexate (3), Diclofenac (1), Yellow fever vaccine (1)
Haemolysis	5	Dapsone/chlorproguanil (5)
Angioedema	4	Pyrimethamine/sulfadoxine (1), Zidovudine/nevirapine/lamivudine (1), Cefalexine (1), Erythromycin (1)
Dyskinesia	3	Amodiaquine (2), Metoclopramide (1)
Epidermal necrolysis	3	Efavirenz (1), Phenytoin (1), Zidovudine/nevirapine/lamivudine (1)
Face oedema	3	Diclofenac (1), Cotrimoxazole (1), Paracetamol (1)
Peripheral neuropathy	3	Stavudine (2), Nevirapine/lamivudine/stavudine (1)
Oedema mouth	3	Artesunate (1), Pyrimethamine/sulfadoxine (1), Paracetamol (1)
Thrombocytopenia	3	Meropenem (3)
Aggressive reaction	2	Ceftriaxone (1), Efavirenz/tenofovir (1)
Dystonia	2	Metoclopramide (1), Guaifenesin (1)
Hyperkinesia	2	Ceftriaxone (1), Hydrochlorothiazide/amiloride hydrochloride (1)
Hyperpyrexia	2	Cefuroxime (2)
Skin exfoliation	2	Cefuroxime (1), Clavulanate potassium/amoxicillin trihydrate (1)
Acute renal failure	1	Gentamicin (1)
Lactic acidosis	1	Zidovudine/nevirapine/lamivudine (1)
Anaemia aplastic	1	Zidovudine (1)
Corneal ulceration	1	Amodiaquine/artesunate (1)
Deafness	1	Cefuroxime (1)
Dementia	1	Ceftriaxone (1)
Epistaxis	1	Furosemide (1)
Haemolytic-uraemic syndrome	1	Dapsone/chlorproguanil hydrochloride (1)
Hallucination	1	Cefuroxime (1)
Melaena	1	Nevirapine (1)
Neuritis	1	Nevirapine/lamivudine/stavudine (1)
Oesophageal ulceration haemorrhagic	1	Sodium bicarbonate (1)
Polyuria	1	Zidovudine/nevirapine/lamivudine (1)
Purpura	1	Artemether/lumefantrine (1)
Skin ulceration	1	Metamizole (1)

4.3.6 ADR outcomes

The ADR outcomes for the reports are shown in Table 4.6. Fourteen reports had more than one ADR. 21 (7%) of the children died. 145 children made a full recovery, and the outcomes in 65 children were not specified.

Table 4. 6: Outcomes for the reports

Outcome	Reports (n)	%
Died	21	7
Not recovered	6	2
Recovered	145	47
Recovered with sequelae	3	1
Recovering	23	7
Unknown	48	15
Unspecified	65	21

4.3.7 Suspect drugs

A total number of 308 drugs were reported for the 297 children. Some reports contained more than one suspect drug, and drugs in these reports were considered separately; hence there are more drugs than the number of reports. Antiretrovirals, antibiotics and antimalarials were the most frequently reported class of drugs (Table 4.7). Vaccines were the 4th most frequently reported class of drugs. These were made up of 'herbal extracts' and 'calcium phosphate/coffea arabica/matricaria recutita/atropa belladonna', reported in 9 cases.

Table 4. 7: Drug Class (preferred base names) and Number of reports

Medicine class	Number of reports (n)	%
Antiretrovirals	74	24.0
Antibiotics	71	23.1
Antimalarials	60	19.5
Vaccines	33	10.7
Analgesics	17	5.5
Antiepileptics	9	2.9
Herbal products	9	2.9
Antineoplastics	7	2.3
Anti-inflammatory	6	2.0
Others	22	7.1
Total number of drugs	308	100

Among the antiretrovirals, nevirapine, lamivudine and zidovudine were the most frequently suspected individual drugs. 30 children experienced ADRs due to meningococcal vaccine. Cotrimoxazole and ceftriaxone were mostly reported among the antibiotics, and for the antimalarials, the children experienced more ADRs with dapsonе/chlorproguanil hydrochloride and artesunate (Table 4.8).

Table 4. 8: Fifteen individual drugs with most reported ADRs

Drugs	Number of reports (n)
Nevirapine	52
Meningococcal vaccine	30
Lamivudine	25
Zidovudine	24
Cotrimoxazole	17
Dapsone/chlorproguanil hydrochloride	11
Ceftriaxone	10
Zidovudine/nevirapine/lamivudine	9
Artesunate	9
Cefuroxime	9
Stavudine	8
Calcium phosphate/coffee arabica	8
Amodiaquine/artesunate	6
Metamizole	6
Methotrexate	6
Others	5 and below

4.3.8 Suspect drugs and severity of ADRs

Forty-four (44) children corresponding to 14.8% of the total number of reports experienced ADRs assessed as serious. There were 21 cases of death, and 7 reports had life threatening ADRs. More ADRs were associated with death reports than those linked with hospitalisation, disabling/incapacitating and life threatening criteria (Table 4.9).

Table 4. 9: Severity of ADRs

Severity	Number of reports
Death	21
Life threatening	7
Caused/prolonged hospitalization	5
Disabling/incapacitating	1
Unspecified severity	10
Total	44

The 44 children had a total of 60 serious ADRs. Seventeen (28%) of the ADRs were reported for antibiotics. These were mainly ceftriaxone and cefuroxime reported for children aged 28 days to 23 months and 2 – 11 years. No serious ADRs due to antibiotics were reported for children 12 – 17 years. Analgesics were associated with 18% of the total serious ADRs reported, and these were reported mainly for infants and adolescents. Antimalarials, mainly amodiaquine, arthemeter and dapson/chlorproguanil, were associated with 15% of the serious ADRs. Herbal remedies were associated with anuria, which made up 12% of the serious ADRs. Vaccines were associated with only two serious ADRs, diarrhoea and vomiting reported for a 50-day old female child.

4.3.9 Drug causality assessment for serious ADRs

The causality assessments for the serious ADRs are shown in Table 4.10. Majority of the 60 ADRs assessed for severity were considered possibly related to the drugs.

Table 4. 10: Causality assessment for serious ADRs

Assessment	ADRs (n)
Certain	6
Possible	32
Probable	11
Unlikely	4
Unspecified	7
Total	60

Five cases, with a total of 6 (10%) ADRs, were assessed as certainly related to paracetamol/diphenhydramine hydrochloride (diethylene glycol), ceftriaxone and the herbal medicine, calcium phosphate/coffea arabica/matricaria recutita/atropa belladonna. All these ADRs led to a fatal outcome. Eighteen percent of the serious ADRs were assessed as probably related to the drugs, and assessment was not specified for 7 (12%) of the ADRs.

4.3.10 Death reports and suspected medicines

There were 21 fatal reports for children age between 6 days and 12 years in this population. A teething mixture of paracetamol/diphenhydramine hydrochloride which was contaminated with diethylene glycol was associated with 4 fatalities, resulting from acute renal failure. The other classes of medicines implicated in death of the children were antibiotics (4), herbal medicines (3), analgesics (3), antimalarials (2) and antiretrovirals (2). The other fatalities were associated with dactinomycin (1), sodium bicarbonate (1)

and phenytoin (1) (Table 4.11). All the children who died while on calcium phosphate/coffee arabica/matricaria recutita/atropa belladonna (herbal medicine) were between the ages of 6 months and 1.3 years, and suffered anuria. Metamizole administered intramuscularly, was associated with injection site pain and death as an event (sudden death). Among the antibiotics, ceftriaxone was implicated with anaphylactic reaction which resulted to the death of an 8-days old male child. The only sedative (diazepam) reported was administered together with pentazocine (analgesic), and both were associated with cardiac arrest which led to the death of a 5-year old male child.

Table 4. 11: Death reports and suspected medicines

Patient	Age	Sex	Suspect drugs	Route	Causality	ADRs	Comments
1	10 months	M	Diethylene glycol	Oral	Probable	Renal failure acute	Contaminant in teething mixture (Paracetamol/Diphenhydramine HCL) for Fever of unknown origin
2	11 months	M	Diethylene glycol	Oral	Possible	Renal failure acute	Contaminant in teething mixture (Paracetamol/Diphenhydramine HCL)
3	14 months	F	Diethylene glycol	Oral	Probable	Renal failure acute	Contaminant in teething mixture (Paracetamol/Diphenhydramine HCL) for Fever of unknown origin
4	17 months	F	Diethylene glycol	Oral	Certain	Renal failure acute	Contaminant in teething mixture (Paracetamol/Diphenhydramine HCL)
5	6 days	F	Ceftazidime	Intravenous drip	Unlikely	Ceased cardiac activity	Antibiotic
6	8 days	M	Ceftriaxone	Intravenous drip	Certain	Anaphylactic reaction	Antibiotic
7	11 months	M	Meropenem	Intra-articular	Possible	Convulsions, thrombocytopenia	Antibiotic
8	6 years	M	Cotrimoxazole	Oral	Possible	Steven Johnson syndrome	Antibiotic
9	22 days	F	Calcium phosphate/coffea arabica/matricaria recutita/atropa belladonna	Oral	Certain	Anuria	Herbal medicine
10	11.5 months	M	Calcium phosphate/coffea arabica/matricaria recutita/atropa belladonna	Oral	Certain	Anuria	Herbal medicine

Table 4.11: Death reports and suspected medicines continued

Patient	Age	Sex	Suspect drugs	Route	Causality	ADRs	Comments
11	1.3 years	M	Calcium phosphate/coffea arabica/ matricaria recutita/atropa belladonna	Oral	Certain	Anuria	Herbal medicine
12	5 years	M	Pentazocine, diazepam	Oral	Possible	Cardiac arrest	Analgesic, psycholeptic
13	12 years	F	Metamizole	Intramuscular	Not specified	Injection site pain	Analgesic
14	12 years	F	Metamizole	Intramuscular	Probable	Sudden death	Analgesic for unspecified pain
15	7 months	F	Dihydroartemisinin	Oral	Unlikely	Renal failure acute	Antimalarial
16	7 years	-	Amodiaquine, artemether	Oral	Possible for all	Angioedema, pruritus, urticaria, lymphadenopathy	Antimalarial
17	4 years	F	Nevirapine	Oral	Possible	Stevens Johnson syndrome	Antiretroviral
18	10 years	F	Stavudine	Oral	Possible	Neuropathy peripheral	Antiretroviral
19	2 years	M	Dactinomycin	Oral	Possible (1), Probable (2), Unlikely (3)	Rash(1), skin discolouration (3), diarrhoea (2), vomiting (3), gingival bleeding(2)	Antineoplastic
20	3 years	M	Sodium bicarbonate	Oral	Probable	Oesophageal ulceration haemorrhagic	Blood forming/blood related product
21	12 years	M	Phenytoin	Oral	Possible	Bullous eruption	Antiepileptic

4.4 DISCUSSION

4.4.1 Reporting rate

Adverse drug reaction reporting is relatively new in Nigeria, and not many reports were received by the pharmacovigilance centre during the first few years of its existence. This is expected of a new system, in addition, underreporting of ADRs has been recognised globally [196]. During the period from 2005 to 2012, a total number of 5080 reports were received, and 297 (6%) were for children age between 0 – 17 years.

The average reporting rate of 0.4 reports per million children per year recorded in this study is very low, and not comparable with the rates from other countries where the reporting system has developed. The rate reported in this study was much lower than those found in the paediatric studies reviewed from Europe, North America, Latin America and Asia. The reporting rate in these studies ranged between 11 – 1458 reports per million children per year. These countries have a developed system of ADR reporting. The highest rate of 1458 was from Cuba, where healthcare professionals are being educated and periodically sensitised to report ADRs [113]. To encourage the reporting of ADRs, the NPC in 2013 made available a toll-free telephone number for consumers to use and report adverse reactions to the pharmacovigilance centre [190] as part of the drive to improve reporting rate.

4.4.2 Age group and sex

In this study, 56% of the reports were for boys. This proportion is consistent with an earlier study from Spain (55%) [81] and Sweden (56%) [235], and that reported for national ADR databases (55%) in a qualitative review of empirical studies about adverse drug reactions in children [23]. The children in age group 2 – 11 years had more ADR reports (57%), which was comparable with a Spanish study [107]. However, other previous studies have reported higher number of ADRs for children 11 – 17 years old [30, 81]. In Sweden [80] and Denmark [79], children 0 – 4 years had more ADR reports, the majority of which were reactions experienced due to vaccines.

4.4.3 Reporter type

In this study, the NPC received almost the same share of reports from physicians (22%) and other healthcare professionals (23%). The highest numbers of reports (49%) were sent by pharmacists, as was also the case in the adult reports. This finding contrasted sharply with the paediatric studies reviewed, where physicians made up between 31 – 89% of the notifiers and pharmacists ranged between 1 – 24% of the reporters. The high number of pharmacists' reporters may likely be due to the ease of patients' access for consultation. In Nigeria, research has suggested that physicians were willing to improve on their ADR reporting knowledge [182], and this could increase the number of reports they send to the NPC.

4.4.4 ADRs and drug class

ADRs were most frequently associated with the skin organ in this study. This was also observed in some of the studies reviewed in Europe [81, 105, 106], China [114], and in a previous single centre Nigerian study [183], where rash was reported as the most common ADR. In contrast, other studies reviewed in Spain [107], Cuba [50] and Sweden [80] have reported pyrexia, drowsiness and application site reaction respectively as the most common ADRs.

The proportion of serious ADRs observed in this study was comparable with that reported for the study in Sweden (13% v 14%) [80]. However, it is lower than the proportion reported in Spain (37%) [107], Denmark (42%) [79] and USA (61%) [30].

Antiretroviral agents were the group of drugs most frequently reported with the ADRs. This observation contrasted with majority of the results reviewed in the studies conducted in Europe and Latin America, where vaccines and antibiotics were mostly associated with the ADRs. The studies conducted in North America showed isotretinoin and medicines used for treating ADHD were the most frequently reported drugs. The high number of antiretroviral related ADRs may likely be due to the number of reports submitted for HIV/AIDS sufferers in Nigeria.

Antimalarials were the second highest drug class reported, and these were linked with almost the same proportion of ADRs as for antibiotics in this study (25.4% v 25.6%). The high proportion of antibiotics and antimalarials observed in this study is likely to be due to the high prevalence of infectious diseases, especially malaria in Nigeria. Therefore the number of ADRs

associated with antibiotics and antimalarials is expected in this study, due to the frequent use of these medications in this population [236].

4.4.5 Causality

In this study, the majority of the reactions were considered possible (55%), and 18% probable. This observation was comparable with the causality assessment reported in a Swedish study of one-year survey of spontaneous reports in which 100 (63.3%) and 56 (35.4%) out of 158 ADRs were respectively assessed as possible and probable, and 2 (1.3%) ADRs were assessed as certain [235]. However, the observation contrasts with the report from the study in Cuba [113] where the majority of the ADRs were classified as probable, and only one ADR was assessed as certainly related to the drug. Causality assessment largely depends on the knowledge of pharmacology of the drugs, de-challenge and re-challenge outcome of the ADRs, as well as concomitant medications administered at the time of the reaction. The WHO-Uppsala Monitoring Centre (UMC) criteria [9] was used in assessing causality of the drugs in all of these studies.

4.4.6 Drug toxicity

There is limited data in the literature on antiretroviral toxicity in children. In this study, antiretrovirals were reported more than any other class of medicines. Nigeria has the highest number of people living with HIV/AIDS in West Africa, and the World Health Organization has estimated that 260,000 children are living with the disease [237], with peak sero-positivity for the virus reportedly occurring in 6 – 8 year olds [238]. Nevirapine was linked with seven out of the

14 cases of Stevens Johnson syndrome (SJS) in this study, one of which was fatal.

In the previous chapter of adult reports, most of the fatalities resulting from Stevens Johnson syndrome were linked to nevirapine and cotrimoxazole. Nevirapine has been associated with SJS in children [239] and adults [214, 240] with the human leukocyte antigens Bw44, HLA-B12 and HLA-DQB1*0601 predisposing to this ADR [212]. It is not known if any of the patients in this study were carriers of these antigens. Other drugs associated with SJS in this study were cotrimoxazole, carbamazepine and phenytoin, and they have all previously been reported as causing SJS in children [241].

Antiepileptic drug-induced SJS has been strongly linked with HLA-B*1502 (HLA-B75) human antigens [242], and we are unable to determine if this was the case in the affected children in this study. Further pharmacogenetic studies to investigate these associations in our particular population would be appropriate.

Nigeria is located in the tropics where malaria is endemic. It currently holds the largest share of the world's burden of malaria, with an estimated 300,000 deaths annually [243]. A higher proportion of reporting for fatalities were associated with antimalarials, compared with the adult reports (10% v 8%). Dapsone/chlorproguanil was developed as a low-cost antimalarial for sub-Saharan Africa [244]. It was implicated in six critical ADRs, haemolysis (5 cases) and haemolytic-uraemic syndrome (one case), in 2005 in this study. However, due to concerns about safety in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, it was withdrawn in 2008 [245].

Similar studies in the literature have not reported on ADRs associated with antimalarials. This could be attributed to the fact that malaria is mainly a tropical disease, and almost all the paediatric studies reviewed in Chapter 2 were conducted in high income countries. However, sudden death, which was reported as the ADR in two children, was associated with the antimalarial, mefloquine in the Spanish study [107]. The frequency of reports associated with antimalarials could be attributed to the ease with which they are obtained by patients from medicine stores for self-medication [246].

Analgesics were associated with three of the fatalities reported; metamizole (dipyrone) was responsible for two of these. In many countries, metamizole has been withdrawn due to its poor safety profile. It is widely used in parts of Africa [247], but has been banned by NAFDAC in Nigeria in 2005 [177]. It is possible that the fatalities arising from metamizole in this study were part of the reports that led to its ban, as the two children were administered metamizole in 2004.

4.4.7 Deaths reported

There were 21 (7%) fatalities out of the total number of cases described in this study. The fatality rate observed in this study was higher than the rates observed in the paediatric studies reviewed. In Europe, the rate ranged between 0.1 – 2.2%, Latin America, 0.2 – 1.6%, and 0.3% in Asia. However, it was lower than the rates from the North American studies, where the average was 8.1%. The contrasting results may likely be due to the large number of reports in the North American studies. Factors that may contribute to the high rate in this study could be the use of counterfeit, substandard or herbal

medicines that is widespread in Nigeria [148]. However, it is not possible to determine if this is the case as such information about the genuineness of medicines was not included in the data analysed.

This issue is highlighted by the majority of the fatalities being associated with contaminated teething mixtures, compared with the adult reports where antiretroviral drugs were mostly implicated. Acute renal failure resulting from the use of paracetamol/diphenhydramine hydrochloride (teething mixture) led to the death of 4 children aged between 28 days and 23 months. The paracetamol/diphenhydramine hydrochloride was initially implicated as the cause of the deaths. However, further investigations by the regulatory agency revealed that the teething mixture (My Baby Teething Mixture) was contaminated with diethylene glycol, and was subsequently banned in 2008 [176].

Diethylene glycol was wrongly used as a solvent in the preparation of the mixture, and it has been reported widely to be associated with acute renal failure in children [248, 249]. The number of deaths attributed to the 'My Baby Teething Mixture' has been reported differently at various times and at different places in Nigeria. In Jos, northern part of Nigeria, a total of 47 children died from diethylene glycol poisoning in 1990 [250], and the death of another 34 children was reported in November 2008 [251]. The risk associated with use of counterfeit and substandard medication is enormous, and similar deaths linked to diethylene glycol have earlier been reported in South Africa [252], Bangladesh [253], Haiti [248] and India [254].

In spite of the large number of diethylene glycol fatalities reported both in the media and published literatures, only a few (4) were entered into the national ADR database. Presently, the agency's yellow form is designed only for reporting adverse drug reactions and not events of this nature; therefore inclusion of a section for capturing these kinds of events is worth considering. The database will be a useful source for national health statistics and planning if all reports of this nature are included and regularly analysed. Strict regulatory control by the relevant agency is therefore required to minimise the risk involved with use of such dangerous excipients for manufacturing medicines, and marketing of counterfeit and substandard finished products.

The use of complementary and alternative medicines (herbal remedies) is prevalent in developing countries. Herbal remedies have been used for disease conditions like epilepsy in Nigeria, and are usually the first choice for treatment, as they are thought to be of natural origin and have more beneficial effects than orthodox medicines [255]. In this study, it was observed that calcium phosphate/coffee arabica/matricaria recutita/atropa belladonna administered as a teething powder was causally related to anuria with certainty, and this led to death of 3 children aged between 6 months and 1.3 years. In the adult report, herbal pollen extracts was associated with one death which resulted from hepatocellular damage. Calcium phosphate/coffee arabica/matricaria recutita/atropa belladonna is a herbal remedy, formulated to relieve pain and irritability from teething, and has not been scientifically tested [256]. The alkaloids in one of the components of this herbal remedy, atropa belladonna possess anti-cholinergic properties [257], and have been used as premedication in anaesthesia [258]. However, adverse effects resulting from

accidental ingestion of the fruit by children has led to seizures [259], irritability, tachycardia, and erythematous flushed skin [260] and anti-cholinergic syndrome [261] which include decreased urination. In 2010, the FDA issued a warning to consumers [262], of serious adverse events it has received for children taking this herbal remedy (Hyland's Teething Tablets) produced in the US. However, child death from anuria, as a consequence of taking this product, has not been reported in the literature. The cases observed in this study may be attributed to atropa belladonna in the teething tablets, and further research is therefore recommended to confirm this.

There are many of such remedies in the market, and patients may have died from their use, especially in developing countries. There are calls for their strict monitoring by the drug regulating agencies, as practiced in the UK when the MHRA extended its Yellow Card Scheme in 1996 to include reporting of suspected adverse reactions to herbal products. The MHRA frequently remind healthcare professionals to report suspected adverse reactions to herbal products irrespective of whether it is licenced or not, and regularly provide updates of such reports in the Agency's website [263].

A high incidence of ceftriaxone related fatalities has been reported in China [264]. The simultaneous administration of ceftriaxone and calcium containing intravenous fluids caused potential serious adverse drug reactions which were reported in the FDA adverse event reporting system [265]. In this study, ceftriaxone was responsible for 10 reports. This included an 8-day old neonate with a fatal outcome that resulted from anaphylaxis. It could not be determined if the event was as a result of drug interaction between ceftriaxone and

calcium as this information was not provided in the database, and no report of concomitant medication was received by this child as the cases reported to the FDA. Anaphylactic shock leading to death of a 1-month old female child on ceftriaxone had also been reported in a previous study in Cuba, and it was also not stated if the child had calcium containing fluids together at the time of this reaction [113]. All the cases received by the FDA were unsolicited reports which concerned 7 infants with fatal outcomes, and these events led to package changes of ceftriaxone.

Metamizole (dipyrone) has at various times been banned due to adverse reactions attributed to it, especially dipyrone related agranulocytosis [266]. In this study, it was observed that 2 children aged 12 years died from metamizole, one from injection site pain, and the other experienced sudden death as an event. The ADRs experienced by these two children were different from the event of toxic epidermal necrolysis attributed to dipyrone when it was banned in 2005 [176, 177]. However, dipyrone is still used in some countries such as Brazil and most part of Europe [267] for the treatment of acute primary headaches [268].

The combination of the analgesic effect of pentazocine and tranquilizing effect of diazepam have been successfully used as anaesthesia for children [269]. In this study, both medications were received orally by a 5-year old male child who later died from cardiac arrest. The event of cardiac arrest was assessed as possibly related to both pentazocine and diazepam, and the indication for use of these medications was not specified. Information such as drug dechallenged and rechallenged outcome of ADRs were conspicuously missing

in the database, and this makes it difficult for the evaluation of causality of the drugs. Other important data elements indicated by 'null' were not provided for some of the descriptors such as type of reporters, severity criteria, outcome of ADRs and drug causality. However, similar findings have been reported in an earlier study in Canada [30], where outcomes for ADRs were not defined in the database reports received in 1998.

4.5 CONCLUSION

This was a descriptive study of children reports in the Nigerian ADR database to provide an insight into the common types of drugs and ADRs reported for children. The ADR reporting rate was low; there were more reports for boys than girls. The most frequent classes of drugs reported were antibiotics and antimalarials, and antiretrovirals and vaccines were the 3rd and 4th most reported. The majority of ADRs reported belong to the system organ class of skin and appendages disorders, and children between the ages of 2 – 11 years had more reports than the other age groups.

In a study of this nature, it was not possible to access the original individual case safety reports. Consequently, one is dependent upon the ADRs being correctly diagnosed, reported and coded. Pharmacovigilance is in its formative years in Nigeria, and the reporting rate of ADRs is low. However, in the last few years of the study period, a steady increase in the number of reports was observed. A high fatality rate was recorded during the study period, mostly reported with herbal products and suspected counterfeit and substandard medications.

CHAPTER FIVE

ADVERSE DRUG REACTIONS IN GHANAIAN ADULTS (18 years and above)

5.1 INTRODUCTION

Ghana is a lower middle income country and has several problems with medicine use [162, 270]. The majority of drugs used are manufactured in foreign countries and the safety of the excipients, diluents, binders, stabilisers and other additives used to prepare the medicines are not known. The quality of these drugs depends largely on selecting the right amount of active ingredients and the other components needed to make the drugs. As already established, no drug is free from adverse reactions.

The diseases experienced in Ghana are not the same as those from other countries, and therefore the reported ADRs will also be different. It was the first country in West Africa to join the International Adverse Drug Reaction Monitoring Programme and maintains a database of ADR reports which has not been analysed. In this chapter, ADRs for adults aged 18 years and above will be described, and those for children 0 – 17 years old will be reported in chapter 6.

5.1.1 Healthcare in Ghana

Ghana is in West Africa, and its population is currently estimated at 25 million, made up of 49% males and 51% females [271]. The public healthcare service in Ghana is decentralised into regional, district and sub-district levels, and services are provided in regional, district hospitals and health centres

respectively [272]. Healthcare service is also provided by private-for-profit healthcare practitioners, Christian missions (private non-profit agencies) and traditional healers. There is a National Health Insurance Scheme (NHIS) in Ghana where a broad range of healthcare services are provided to Ghanaians through mutual and private health insurance scheme [273].

The scheme is not free and annual premium range between 7.2 and 48 Ghana cedi (£1.03 and £6.09), depending on income and ability to pay [274, 275]. Registered members of the scheme contribute towards outpatient and most in-patient services, diagnostic testing, specialist care, most surgeries, oral health treatments, emergency care, all maternity care services (including Caesarean deliveries), and all drugs in the NHIS Medicines List [276]. According to the annual report of the National Health Insurance Authority for 2012, active membership of the scheme was 8,885,757, representing 35% of the population [277]. The scheme enables registered members to seek formal healthcare when they are ill [278]. The Ghana healthcare system is under the jurisdiction of the Ministry of Health, which is also responsible for control of drugs. The majority of Ghanaians, mostly the poor, pay out of their own pockets to access medical care [279].

5.1.2 Disease burden in Ghana

The most common diseases in Ghana include those that are endemic to sub-Saharan African countries. Cardiovascular diseases and cancer are responsible for the majority of the deaths in Ghana (Table 5.1).

Table 5. 1: Major causes of deaths in the general population [134]

Causes of death	Per 100,000 of population
Cardiovascular diseases	343
Cancer	127
Malaria	109
HIV/AIDS	89
Tuberculosis in HIV-positive people	38
Tuberculosis in HIV-negative people	14.2

In the last few decades, non-communicable diseases such as hypertension, stroke, diabetes and cancers have become the top 10 causes of death [280], and account for an estimated 42% of total deaths [281]. However, malaria, HIV/AIDS, diarrhoeal diseases, lower respiratory infections, and perinatal conditions account for 50% of all deaths [282]. Malaria is also a leading cause of death in Ghana, as in Nigeria. According to Ghana government statistics, 45% of all outpatient hospital visits were malaria-related. Among pregnant women, malaria accounted for 14% of outpatient hospital visits, 11% of admissions and 9% of deaths [283]. In contrast to Nigeria, it is responsible for 60% of outpatient visits to health facilities, 30% childhood deaths, 25% of deaths in children under one year and 11% of maternal deaths [131]. Tuberculosis is among the six killer diseases in Ghana [284], and due to the poor economic status of most infected people, treatment at health centres in the country is free [285].

Other common diseases included vaccine preventable infections such as cholera, typhoid, pertussis, tetanus, chicken pox, yellow fever, measles, and

infectious hepatitis. Immunisation programme to protect children and pregnant women against these diseases was initiated in 1978 [286]. HIV/AIDS prevalence in Ghana was estimated as 2.1%, with 18,000 dying of the disease in 2012, compared to 240,000 deaths in Nigeria [129]. Among the age groups, the 35 – 39 year olds had the highest prevalence of 3.3% [287].

Diabetes is a major non-communicable disease in Ghana [288]. The prevalence of diabetes in 2012 was reported as 8% [289]. However, diabetes mortality, morbidity and disability data are lacking, and there are no guidelines for diabetes care for the various healthcare levels [290]. In 2008, WHO estimated that 650,000 of 21.6 million people living in Ghana suffered from severe mental disorder, and a further 2,166,000 had moderate to mild mental disorder [291].

Even though Ghana and Nigeria are located in the same zone in sub-Saharan Africa, disease prevalence in the two countries are different. Communicable diseases, maternal, perinatal and nutritional conditions are responsible for 51 percent of all mortality in Ghana [281], compared to a higher proportion (67%) in Nigeria [130].

5.1.3 Drug use in Ghana

A National Drug Policy is in operation in Ghana where guidelines for prescribing and dispensing of medicines by qualified professionals are stipulated, including patient compliance with medications. Treatment guidelines are systematically developed statements about the current use of

drugs that assist prescribers in deciding on appropriate treatments for specific clinical conditions. The development of these guidelines is important for health systems particularly in developing countries with limited resources and growing health needs [292]. Therefore, policy makers in Ghana engage in designing cost effective measures that ensure accessible and affordable healthcare for all, particularly the poor and vulnerable groups such as pregnant women and children.

In order to achieve this goal, an essential medicines list was developed based on the WHO Model List of Essential Medicines [293]. Consequently, drugs in the Ghana National Health Insurance Scheme Medicines List for treatment of health problems were derived from this. The drugs selected are based on results of efficacy and safety evaluations obtained from controlled clinical trials and on the performance in general use in a variety of medical settings. When several drugs are available for the same condition, only the drug that provides more convenient benefit/risk ratio is selected [294].

The decision by medical practitioners and drug prescribers to provide appropriate treatments for specific clinical conditions is enhanced by the treatment guidelines. They are powerful tools in promoting the rational use of medicines, when used together with a national list of essential medicines. The guidelines and essential medicines list offer an opportunity to ensure that training of health workers is based on a logical approach to treatment and on a consensus about the selection of essential medicines. Treatment guidelines are used for in-service training, supervision and medical audit, and are also an excellent basis for pharmaceutical supply in the public sector

[295]. When standard treatment guidelines are properly developed and implemented, total cost of treatment is lowered and patients' clinical outcomes are improved [296]. Non-implementation of the standard treatment guidelines for the most common diseases in developing countries is one of the causes of irrational drug use [297].

The National Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) are in operation in Ghana. The first edition of the guidelines was published in 1988 as Essential Drugs List and National Formulary with Therapeutic Guidelines [298, 299]. The guidelines were separated into STGs and EML and published individually in 2004 and the current sixth editions were published in 2010. Recommendations in the STG specify how adults and children should be managed and treated for each disease condition [300]. In spite of the presence of the guidelines in Ghana, drugs such as antibiotics [270] are used irrationally through self-medication, and off-labelled medicines are prescribed for patients diagnosed with various mental conditions, such as schizophrenia, epilepsy and mood disorders [301].

Malaria is endemic in Ghana. Evidence shows that recommended guidelines for prescribing Artemisinin – based Combination Therapies (ACTs) for confirmed uncomplicated malaria have not been followed [302]. However, it has been reported that adhering to guidelines and rational prescribing of antimalarials resulted in fewer deaths of children with malaria [303].

5.1.4 Pharmacovigilance in Ghana

The national drug policy in Ghana also empowered the Ministry of Health to set up and maintain a national centre for pharmacovigilance that was entrusted with the responsibility for drug monitoring to ensure public safety from the hazards of drugs [304].

Pharmacovigilance activities were already in existence in 1992 at the Centre of Tropical Clinical Pharmacology of the University of Ghana. These activities were later recognised in the Ghana National Drug Policy [305], and this led to the establishment of the National Pharmacovigilance Centre (NPC), whose membership of the WHO Programme for International Drug Monitoring began in 2001. Presently, pharmacovigilance activities are carried out by the Safety Monitoring Unit of the Ghana Food and Drugs Authority. ADR reports are received from pharmacovigilance units of health institutions and consumers throughout the country.

In order to meet its mandate, the NPC introduced a system whereby contact persons for pharmacovigilance activities were appointed for each healthcare facility, regional hospitals, clinics and private hospitals to serve as link between the institutions and the NPC. The NPC also has a presence in all the regions in Ghana, which serve as centres for collation of spontaneous reports of ADRs for transmission to the national headquarters.

The Public Health Act 2012, Act 851 makes it mandatory for foreign and local medicine manufacturers in Ghana to report adverse events associated with their products to the Food and Drugs Authority [306]. Reports of ADRs are received from healthcare professionals and consumers, as well as from

marketing authorisation holders of drug products. An advisory/expert committee on pharmacovigilance assesses the reports before they are entered into the pharmacovigilance database, and then transmitted to WHO VigiBase in Uppsala, Sweden (Figure 5.1). The vigilance unit of the Safety Monitoring Department manages and maintains the ADR database, and is responsible for promoting pharmacovigilance activities through education of healthcare professionals and the general public [307].

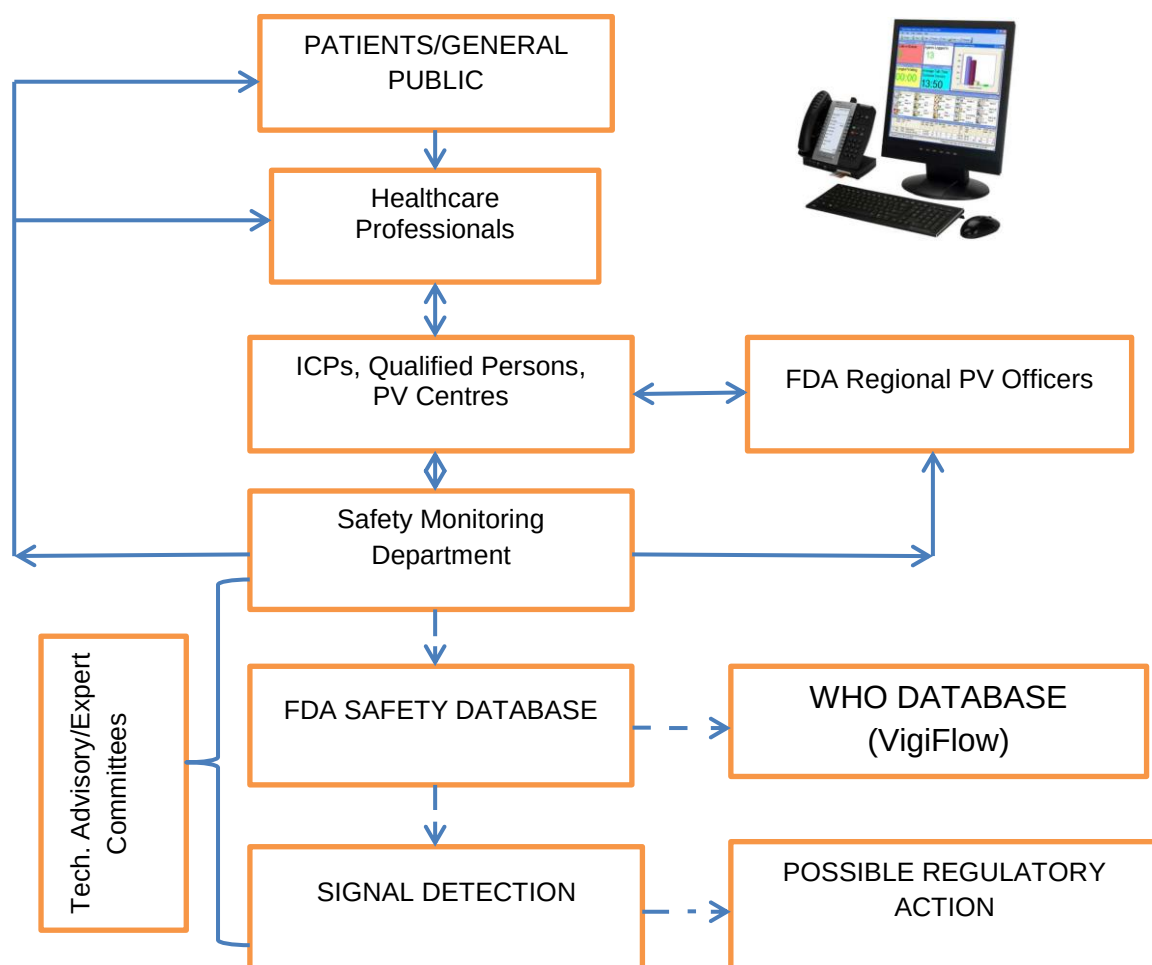


Figure 5. 1: Ghana ADR reporting system (adapted from the National Pharmacovigilance Centre, Ghana)

5.1.5 ADR reporting in Ghana

An assessment of the pharmacovigilance system in Ghana revealed that healthcare professionals are aware of the existence of ADR reporting programme of the Ghana Food and Drugs Authority [308]. Adverse drug reaction reports are mainly submitted to the National Pharmacovigilance Centre by doctors, pharmacists and nurses. The limiting factor of ADR reporting is non-availability of reporting forms and lack of knowledge of the reporting procedures [309]. Marketing authorisation holders of products and consumers also submit reports of ADRs to the health authority. It is important that reporters of ADRs are aware of the right procedures employed in reporting, and the importance attached to pharmacovigilance as already identified in Mozambique [310] and Nigeria [179]. Healthcare professionals need to be able to identify ADRs and report them appropriately.

5.1.6 ADR studies

The monitoring of the safety of specific medicines used for treatment of the common diseases such as pentavalent vaccine [311], rotavirus vaccine [312], and amodiaquine-artesunate vs artemether-lumefantrine [313] and sulfadoxine-pyrimethamine [314] have been conducted in Ghana. Other pharmacovigilance studies included cohort event monitoring in infants receiving malaria intermittent preventive treatment along with routine immunisations [315], and patients receiving treatment for malaria in urban Ghana [316].

5.1.7 Aim

To conduct descriptive analyses of Ghana ADR reports for adults aged 18 years and above in VigiBase of UMC.

5.1.8 Objectives

The main objectives of this research will be to:

- Determine the number of ADR reports received per year
- Identify the types of ADRs and drugs reported
- Identify ADR severity and outcome of reactions as reported
- Identify the suspect drug types with higher number of ADRs
- To identify reports of death and drugs implicated
- Determine if causality assessments of drugs were reported
- Identify the most reported drug classes

5.2 METHODS

5.2.1 ADR data collection

Adverse drug reaction reports in Ghana are received from patients and healthcare professionals using a form provided by Ghana Food and Drugs Authority (See Appendix 4). The form contains similar information as described in Chapter 3 (section 3.2.3) of this report. These forms are distributed to all health facilities, regional hospitals, clinics and private hospitals in all the 10 regions in Ghana by the National Pharmacovigilance Centre (NPC).

5.2.2 Transmission of reports

Reports of ADR(s) from healthcare professionals and the general public including patients are sent to the regional pharmacovigilance centres. These reports are forwarded to the safety monitoring department of the NPC by the contact person for pharmacovigilance. Reports are also sent directly to the headquarters of the NPC by the general public and healthcare professionals.

5.2.3 Report processing

Trained pharmacovigilance personnel review the reports for completeness of required information at the safety monitoring department of the national centre. However, reports without the minimum required information are followed up with reporters by pharmacovigilance qualified persons as required by the WHO International Drug Monitoring Programme. Adverse drug reactions are coded based on WHO Adverse Reaction Terminology (WHO-ART) [192], and are classified into serious and non-serious. The criteria for seriousness of the ADRs are death, life-threatening, required/prolonged hospitalisation, significant disability/incapacity and congenital anomaly/birth defect [193]. The suspect drugs are coded based on WHO Drug Dictionary Enhanced (WHO-DD) [195]. A dedicated committee of experts (Technical Advisory/Expert Committees) regularly meet to assess the reports. The committee determine if a prior temporal relationship exist between the suspect drug and the ADR, evaluate the outcome of the ADR when the suspect drug is dechallenged and rechallenged (when information is available), and also consider age and sex of the patient, to assess causality of the drug using the WHO criteria [317]. All reports meeting the

minimum requirements of reporter, patient details, suspect drug information, and assessed as ADRs by the expert committee are entered into the Ghana Food and Drugs Authority database and forwarded to Uppsala Monitoring Centre.

5.2.4 Data extraction

Application for use of the ADR data was made (see Appendix 5) and an approval was given by the Ghana Food and Drugs Authority (see Appendix 6). Reports submitted to the Uppsala Monitoring Centre from November 1999 to December 2012 were extracted from Vigibase into excel file. The data elements included report number, age and gender of patient, reporter, ADR in WHO-ART preferred term, drug in WHO-DD preferred base name, indication for use, seriousness criteria, outcome of reaction, and causality assessment of the reaction.

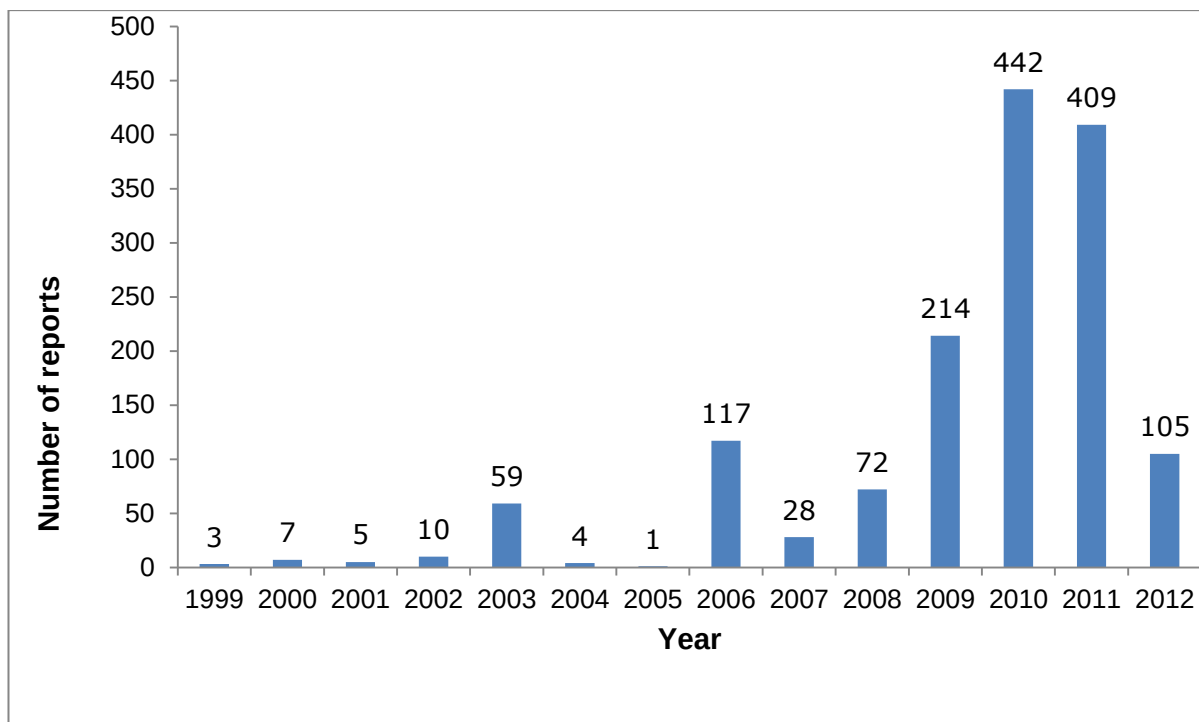
5.2.5 Data analysis

The data was analysed as described in chapter 3 (section 3.2.8).

5.3 RESULTS

5.3.1 Reports by year, sex and age

Over the 14-year period, 1476 reports containing 3639 ADRs were received for 1476 patients. This represented 7.5 reports per million individuals per year, and 2.5 ADRs per report. The number of reports received ranged from 1 to 442 yearly between 1999 and 2012 (Figure 5.2). The highest number of reports, 442 was received in 2010.



Note: Not all the reports received in 2012 were entered into Vigibase when the data was extracted for this study.

Figure 5. 2: Number of reports by year

In the reports where sex was indicated, females were 782 (53%) and males were 659 (45%). Sex was not indicated for a total number of 35 (2%) reports. The reports for age group 18 – 29 years were more than the reports for adults aged 50 years and above (Table 5.2).

Table 5. 2: Number of reports by age

Age group	Number of reports (n)	%
18 – 29 years	425	29
30 – 39 years	327	22
40 – 49 years	284	19
50 – 59 years	205	14
≥ 60 years	144	10
Unspecified	91	6
Total	1476	100

5.3.2 Reporters of ADRs

Pharmacists submitted more reports of ADRs than the other groups. Physicians and other healthcare professionals including nurses submitted almost the same proportion of reports (Figure 5.3). Reporter types were not specified for 74 (5%) of the reports.

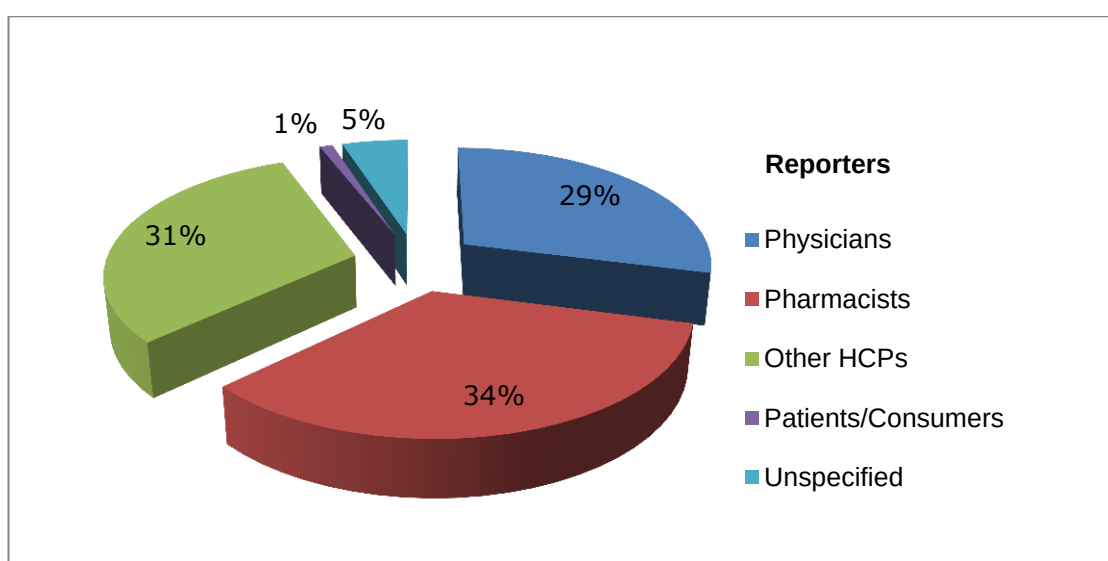


Figure 5. 3: Notifiers and proportion of reports

The highest number of reports 442 (30%) were received in 2010, and 254 (58%) of these were from physicians which was much higher than their submissions in other years (Table 5.3). Notably, pharmacists submitted a high number of reports 125 in 2009 and in 2011, 236 (58%) were submitted from other healthcare professionals including nurses. Other healthcare professionals submitted all the reports received between 1999 and 2002. There were no reports from Marketing Authorisation Holders (MAHs) over the 14 years.

Table 5. 3: Reporters by Year

Reporters	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
	n	n	n	n	n	n	n	n	n	n	n	n	n	n
Physicians	0	0	0	0	53	2	0	17	7	17	30	254	34	12
Pharmacists	0	0	0	0	6	2	1	49	16	27	125	110	122	43
Other HCPs	3	7	5	10	0	0	0	43	5	9	49	45	236	43
Consumers	0	0	0	0	0	0	0	3	0	2	2	2	6	1
Unspecified	0	0	0	0	0	0	0	5	0	17	8	31	11	6
Total	3	7	5	10	59	4	1	117	28	72	214	442	409	105

5.3.3 Adverse drug reactions in system organ class

One in five ADRs involved the skin (21%). General disorders, central nervous system disorders and gastro-intestinal system disorders were the other most frequent disorders (Figure 5.4).

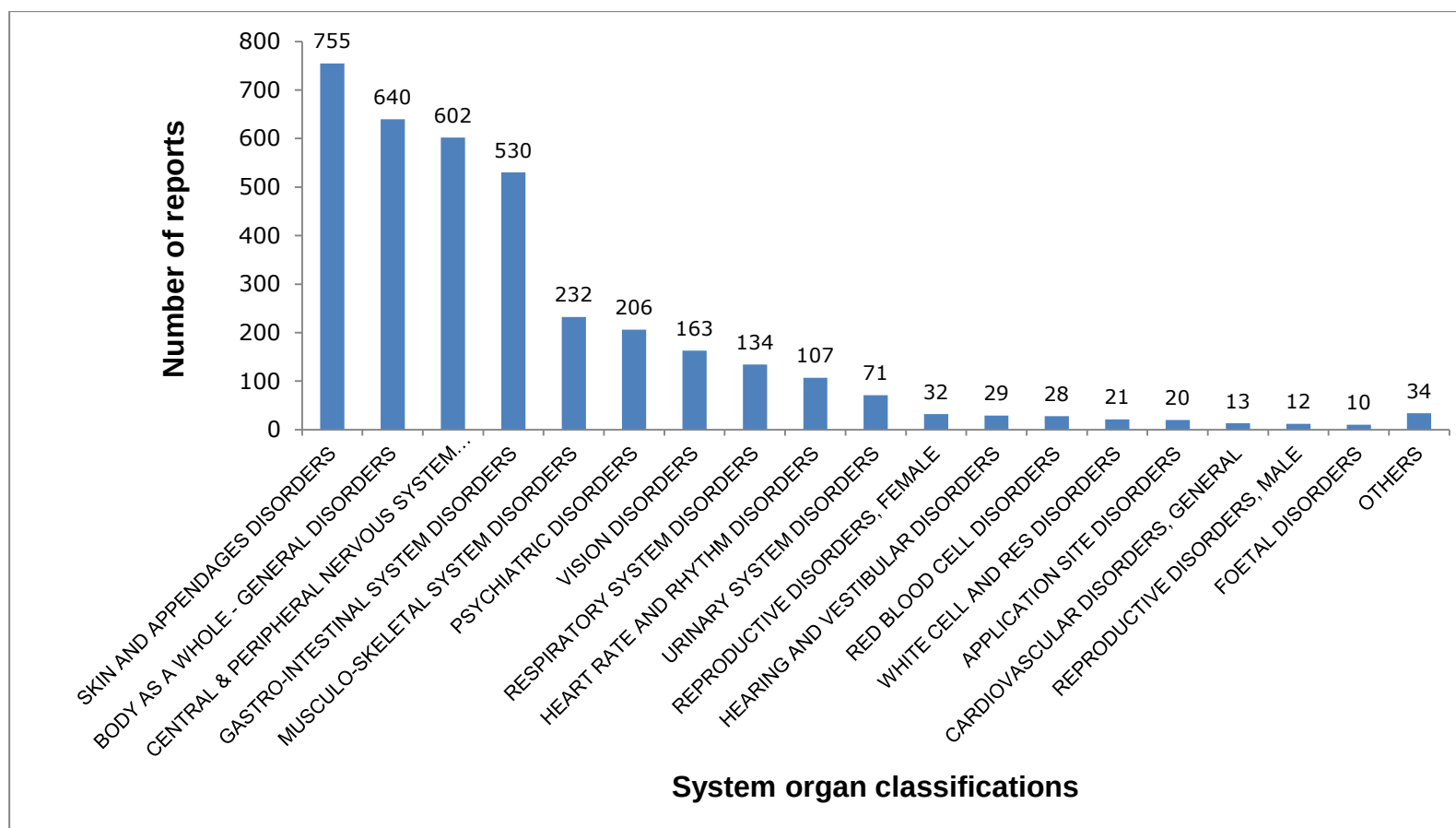


Figure 5. 4: Distribution of ADRs in system organ class

The frequencies of individual ADRs described in preferred terms are shown in Table 5.4. Pruritus, headache, dizziness, and asthenia were the most frequently reported ADRs. Stevens Johnson syndrome was reported 70 (1.9%) times.

Table 5. 4: Most Common ADRs (preferred terms)

ADRs	n	%
Pruritus	326	8.9
Headache	244	6.7
Dizziness	215	5.9
Asthenia	175	4.8
Abdominal pain	141	3.9
Rash	137	3.8
Vomiting	110	3.0
Palpitation	103	2.8
Arthralgia	97	2.7
Myalgia	90	2.5
Back pain	77	2.1
Nausea	74	2.0
Stevens Johnson syndrome	70	1.9
Conjunctivitis	69	1.9
Chest pain	69	1.9
Diarrhoea	68	1.9
Insomnia	59	1.6
Coughing	58	1.6
Agitation	55	1.5
Malaise	55	1.5
Anorexia	54	1.5
Rigors	52	1.4
Urticaria	49	1.3
Face oedema	47	1.3
Eye pain	45	1.2
Dyspnoea	42	1.1
Skeletal pain	35	1.0
Dystonia	34	1.0
Fever	33	1.0
Others	956	26.3
Total	3639	100

5.3.4 Severity of reports

A total of 556 reports were assessed as serious. Of these, the level of severity in 37 reports was not indicated. Of the 519 reports with severity criteria, 26 (5%) were fatal, and these were made up of equal numbers of females and males. There were no deaths reported in 2004 and 2005. The seriousness criterion of hospitalisation was assessed for 394 (76%) of the cases, and of these, 273 (69%) were reported in 2010. The reports assessed as life threatening were 64 (12%), disabling/incapacitating 27 (5%), and other significant made up 8 (2%) of the reports.

5.3.5 Causality assessment of reports

Of the 556 serious reports, 519 (involving 1417 ADRs) were assessed for causality (Table 5.5).

Table 5. 5: ADRs with seriousness criteria and causality assessments

Assessment	ADRs	
	n	%
Certain	204	14
Probable	512	36
Possible	616	43
Unlikely	80	6
Unknown	5	0.4
Total	1417	100

Some examples where the causality assessment was recorded as certain were a patient who died in pain following albendazole, and another who died from convulsions, hypertonia and fever, following risperidone.

5.3.6 Suspect drugs

The total number of suspected drugs in preferred base names was 1799. The first four most frequently reported class of drugs were anti-infectives (Table 5.6). Antimalarials and anthelmintics were the two groups of drugs most frequently associated with the ADRs.

Table 5. 6: Drug Classes and number of times suspected

Drug class	n	%
Antimalarials	494	27.4
Anthelmintics	413	23.0
Antiretrovirals	277	15.4
Antibiotics	217	12.1
Anti-inflammatory	58	3.2
Calcium channel blockers	46	2.6
Analgesics	44	2.4
ACE inhibitors	40	2.2
Anti-protozoals	22	1.2
Vaccines	22	1.2
Antacids	19	1.1
Immunoglobulins (antitoxins)	19	1.1
Vitamins	15	0.8
Antiepileptics	13	0.7
Blood products	12	0.7
Antidiabetics	10	0.6
Others (less than 10)	78	4.3
Total	1799	100

The fourteen most frequently reported individual drugs were anti-infective agents. Amodiaquine/artesunate, amodiaquine and pyrimethamine-sulfadoxine were the most frequently suspected antimalarials. The most frequently suspected anthelmintics were albendazole and ivermectin, and the antiretrovirals were zidovudine/lamivudine, efavirenz and nevirapine. Ciprofloxacin and cotrimoxazole were the most frequently suspected antibiotics (Table 5.7).

Table 5. 7: Individual drugs and number of times suspected

Drugs	Number of times suspected (n)
Albendazole	150
Amodiaquine/artesunate	144
Ivermectin	139
Levamisole	85
Pyrimethamine/sulfadoxine	79
Amodiaquine	77
Artesunate	71
Zidovudine/lamivudine	68
Efavirenz	58
Nevirapine	56
Artemether/lumefantrine	50
Quinine	39
Stavudine	38
Lamivudine	36
Diclofenac	35
Lisinopril	33
Ciprofloxacin	31
Nifedipine	29
Cotrimoxazole	25
Amocarzine	22
Amoxicillin	21
Suramin	20
Gentamicin	19
Snake venom antiserum	17
Amlodipine	16

5.3.7 Outcome of ADRs

There were 26 deaths. 961 patients had completely recovered, 21 patients had not recovered, and 64 patients were recovering from their ADRs (Table 5.8). Unknown outcome was reported for 70 patients, and the outcomes of ADRs for 411 reports were not specified.

Table 5. 8: ADR outcomes for all reports

Outcome	Reports (n)
Death	26
Not recovered	21
Recovered	961
Recovered with sequelae	29
Recovering	64
Unknown	70
Unspecified	411

5.3.8 Drug – related deaths

30 drugs were reported for the 26 fatalities. Albendazole, artesunate, ivermectin and pyrimethamine/sulfadoxine were mostly suspected for the fatal ADRs (Table 5.9).

Table 5. 9: Fatalities and individual drugs

Drugs	Number of times suspected
Albendazole	5
Artesunate	5
Ivermectin	3
Pyrimethamine/sulfadoxine	3
Misoprostol	2
Acetylsalicylic acid/caffeine	1
Acetylsalicylic acid/caffeine/paracetamol	1
Amodiaquine	1
Amodiaquine/artesunate	1
Artemether/lumefantrine	1
Levofloxacin	1
Magnesium sulphate	1
Minerals/herbal products	1
Peginterferon alfa-2a	1
Risperidone	1
Cotrimoxazole	1
Celepid (fat emulsion)	1
Total	30

Stevens Johnson syndrome was the most common cause of the fatalities. Antimalarials were associated with 11 fatalities resulting from Stevens Johnson syndrome (3), foetal death (4), CNS disorders (2), oedema (1) and agitation (1) (Table 5.10). Anthelmintics were involved with 4 fatal cases. An unspecified drug, celepid, considered as fat emulsion was associated with the death of a 73 year old male patient who suffered from diarrhoea. A 49 year old male died from vomiting following an unknown herbal extract.

Table 5. 10: Fatalities reported and suspected drugs

ADRs	Number of Patients	Drugs and number of times suspected
Stevens Johnson syndrome	8	Pyrimethamine/sulfadoxine (3), Acetylsalicylic acid/caffeine (2), Albendazole + Ivermectin (2), Cotrimoxazole (1)
Foetal death	4	Artesunate (4)
Oedema	2	Artemether/lumefantrine (1), Albendazole + Ivermectin (1)
CNS disorders	2	Amodiaquine/artesunate (2)
Agitation	1	Amodiaquine/artesunate (1)
Cardiac arrest	1	Misoprostol (1)
Chest pain	1	Albendazole (1)
Diarrhoea	1	Celepid (fat emulsion) (1)
Convulsions + Hypertonia	1	Risperidone (1)
Liver failure (jaundice)	1	Levofloxacin (1)
Vomiting	1	Herbal/mineral extracts (1)
Uncertain*	3	Various
Total	26	

**Cause of death uncertain*

5.3.9 Critical ADRs

An additional 289 non-serious ADRs were considered as WHO-ART critical ADRs for 276 patients (Table 5.11). Stevens Johnson syndrome, face oedema, angioedema, and dystonia were the most frequently reported critical ADRs.

Table 5. 11: Critical ADRs

Critical ADRs	n	%
Stevens Johnson syndrome	64	22
Face oedema	38	13
Angioedema	31	11
Dystonia	24	8
Mouth oedema	19	7
Skin exfoliation	11	4
Erythema multiforme	9	3
Dermatitis exfoliative	7	2
Peripheral neuropathy	7	2
Bronchospasm	5	2
Dyskinesia	5	2
Generalised oedema	5	2
Decrease hearing	4	1
Polyuria	4	1
Anaphylactic reaction	3	1
Foetal death	3	1
Epidermal necrolysis	3	1
Hallucination	3	1
Photosensitivity reaction	3	1
Purpura	3	1
Others (less than 3)	38	13
Total	289	100

5.4 DISCUSSION

5.4.1 Number of reports

The National Pharmacovigilance Centre was established in 2001, although the data contained reports received in 1999. For the first ten years, less than 120 reports were received annually and only one report was received in 2005. The number of reports increased from 214 in 2009 to a peak of 442 in 2010, and not all the reports for 2012 were entered into Vigibase when the data was extracted for this study. This increase may be attributed to the establishment of a centre of WHO Programme for International Drug Monitoring in Ghana (UMC – Africa), whose role is to provide support for national pharmacovigilance centres in Africa [318]. The activities of the centre which also include the provision of training and resources for monitoring drugs may have impacted positively on the National Pharmacovigilance Centre, which led to increase in the number of reports from 2009.

5.4.2 Notifiers of ADRs

Marketing authorisation holders (MAHs) are obligated to submit reports of ADRs for their products as required in countries like USA, [49], Denmark [58], Czech Republic [83], and generally among the EEA and EU member states of the European Medicines Agency [319]. This regulation was empowered by the Public Health Act, 2012, Act 851, Part 7, Section 125 [306], yet no ADR report was submitted to the NPC during the period under study. The reason for the non-participation of pharmaceutical companies may be attributed to lack of enforcement of the regulation by the Health Authority.

Pharmacists have direct access to patients and have continued to play a major role in the reporting of ADRs [320]. The high number of reports from pharmacists may have included reports from patients/consumers who have contacted them directly for consultation. However, in countries such as The Netherlands [93], Denmark [204] and UK [82] where pharmacovigilance has developed, patients have submitted high number of reports. In Nigeria, a toll-free telephone line has been provided in 2013, to encourage patients/consumers to report ADRs to the National Pharmacovigilance Centre [190].

Physicians reported less ADRs than pharmacists and other healthcare professionals in this study. This observation was consistent with the Nigerian adult reports in chapter 3. However, it is in contrast with reports from the study of the Ethiopian pharmacovigilance database, where physicians submitted majority of the ADRs [101]. Underreporting of ADRs by Ghanaian physicians have been attributed to lack of training in pharmacovigilance [120]. It has been proposed that incentives such as writing pens could be provided to healthcare professionals to encourage reporting [206], and in Canada [321], mandatory reporting of ADRs is being considered for doctors.

5.4.3 Adverse drug reactions

Reactions belonging to skin and appendages disorders were mostly reported in this study, and made up 21% of the total ADRs. This observation was similar to the result of the Nigerian adult study in Chapter 3, and majority of the reviewed studies conducted in Europe and the one from Ethiopia. The individual most reported ADR was pruritus, and was also the case in the Nigerian adult reports.

This differed from other reviewed studies conducted in UK [82] and India [98], where nausea and vomiting were respectively the most frequently reported ADRs. The skin is the largest protective organ of the body, and may be the reason why more reactions are associated to it, particularly in drug allergy [322].

5.4.4 Causality assessment

The assessment of causality is the evaluation of the likelihood that a particular treatment is the cause of an ADR. The Technical Advisory/Expert Committee assessed the association of ADRs and drugs for all the reports by judgement [323], based on clinical-pharmacological aspects of each case, history, quality of data, and grouped the causality as certain, probable, possible, likely, and unlikely according to WHO criteria [191]. Few studies of this nature have described causal relationship between drugs and ADRs for adults. The proportion of ADRs assessed as 'certain' in this study was similar (14% v 14%) to one of the identified studies reviewed in Chapter 2, which was conducted in Korea [51]. Agreement on the assessment of drug causality is not always reached. Where differences exist, knowledge of such factors as temporal sequence, previous information on the drug, dose relationship, response pattern to drug, rechallenge, alternative candidates and concomitant drugs inform the final decision of the Committee.

5.4.5 Drugs

The profile of drugs observed in this study showed antimalarials were the most frequently reported class of drugs followed by anthelmintics and antiretrovirals. The large number of antimalarials reported for the suspected ADRs in this study

reflects the high prevalence of malaria in Ghana [324]. This finding differed from the Nigerian adult report in Chapter 3, and the study from Ethiopia where the prevalence of HIV/AIDS is high [207], and antiretrovirals were the most frequent class of drugs reported [101]. Even though antimalarials made up the largest group of drugs reported, albendazole, ivermectin and levamisole (all anthelmintics), were respectively the first, third and fourth most frequently reported individual drugs. The high number of drugs reported may be due to the prevailing disease conditions in the country, for which the appropriate therapy had been applied.

5.4.6 Drug – related deaths

Deaths resulting mainly from anti-infective agents were reported in 26 cases representing 1.8% of the population studied. This was a lower proportion of the total reports, compared to 2.4% in the Nigerian adult reports. In the studies identified and reviewed in Chapter 2, a high rate of 17.3% was reported in USA in a study conducted using data which was collected for 8 years with 467809 reports [100]. The differences in reported rates may be due to selective reporting, as in the case of the study in USA, where only serious ADRs were described. The number of deaths reported may not be the true reflection of totality of fatalities associated with drugs in Ghana, as not all may have been reported to the NPC.

Malaria poses a major health challenge according to The National Malaria Control Programme in Ghana [325]. When artesunate-amodiaquine combination was introduced in 2005 as first line of therapy for the management of uncomplicated malaria, challenges resulting from adverse events were

reported. This evidence led the authorities to recommend pyrimethamine/sulfadoxine (Fansidar) for intermittent preventive treatment of malaria in pregnancy in 2007 [325].

Pyrimethamine/sulfadoxine is used as a fixed dose combination for the treatment of *P. falciparum* malaria, and has been reported to cause erythema multiforme, Stevens Johnson syndrome and toxic necrolysis [326]. In studies which involve adult western travellers taking pyrimethamine/sulfadoxine prophylaxis for malaria, the rate of cutaneous hypersensitivity reactions has been reported to be approximately one per 5,000 – 8,000, with one fatality per 11,000 – 25,000 individuals [326-328]. Now, it is no longer used as prophylaxis because of the risk of serious cutaneous toxicity [329], and also due to resistance of the malaria parasite and lack of efficacy after 5 years of its shelf life [330, 331]. Pyrimethamine/sulfadoxine was associated with three of the eight fatal cases involving Stevens Johnson syndrome in this study. All three cases involved men aged between 18 and 35 years, and they took pyrimethamine/sulfadoxine for *P.falciparum* malaria, even though it is not recommended for malaria in Ghana (except in pregnant women) [325].

The cause of Stevens Johnson syndrome is unknown, however, it has been suggested that it could be influenced by coadministration with chloroquine [327], ethnic differences in susceptibility [332], genetic predisposition [333, 334], and drug metabolism [335]. Pyrimethamine/sulfadoxine was the only suspect drug reported for the three fatalities, without any concomitant medication. Earlier reports have shown fatalities resulting from Stevens Johnson syndrome following sulfadoxine alone as prophylaxis against cholera in Mozambique [336], and against meningococcal disease in Morocco [337]. It was not possible

to know from the data if the drug was taken as prophylaxis or for treatment of malaria. However, it is known in Ghana that healthcare providers do not adequately implement the guidelines for treatment of malaria, and presumptive diagnosis of malaria is high and can be accompanied by inappropriate prescription practices [302].

Malaria during pregnancy has been associated with mortality and morbidity to the mother and the unborn child [338]. The artemisinin derivatives are now generally used for the treatment of *P.falciparum* malaria, and combination of these treatments are recommended in the second and third trimester of pregnancy [339]. Among the artemisinin derivatives, intravenous artesunate is the drug of choice for the treatment of severe and complicated malaria in adults and pregnant women [340]. Foetal deaths in four individuals resulting from artesunate were observed in this study. This may be attributed to lowered plasma concentrations and very short half-life (<8 h) of artesunate, which has been reported as risky for the life of the pregnant mother and foetus [341]. Although, animal data have suggested an association between artemisinin derivatives with foetal resorption and foetal abnormalities when administered early in pregnancy [342], there is limited data in the literature concerning foetal deaths in relation to artesunate for malaria therapy in pregnant women.

There was one fatality involving celepid in this study. A similar product, 10% soybean oil emulsion (Intralipid*10%) that is properly formulated, is used extensively in Europe for intravenous alimentation and has been clinically evaluated in United States [343]. Its long term use has previously been associated with 'fat overload syndrome' characterised by fever, irritability,

nausea, vomiting and severe anaemia [343-345]. A life-threatening intolerance to the infusion has also been reported in a patient who initially thrived on the soybean oil emulsion [346].

Traditional medicine has played an important role in meeting the demands of primary healthcare in Africa. In Ghana, the introduction of 'on-the-spot-payment' for orthodox healthcare delivery has further increased the patronage of traditional medicine providers by a large number of patients [347], who receive herbal treatment for their ailments. A 49-year old male patient reportedly died from vomiting following an unspecified herbal/mineral extracts in this study, and indication for use of the product was not reported. A number of factors such as contamination, or interaction with other pharmaceutical products makes assessment of adverse effects associated with traditional medicines more complex [348]. There was no concomitant medication administered to the patient along with the herbal product; however, the pharmacovigilance Technical/Expert Advisory committee considered drug causality assessment as possibly related to the event. Even though it was not possible to determine if the source of the product was from a pharmacy practitioner or traditional medicine provider, this reported event underscores the need for healthcare professionals to be more aware of the danger herbal supplements poses to the public.

5.5 CONCLUSION

The data revealed that Ghana began collecting ADR reports in 1999, before it became a member of WHO International Drug Monitoring Programme in 2001. The number of reports significantly increased with the establishment of a centre of WHO Programme for International Drug Monitoring in Ghana (UMC – Africa)

in 2009. The large number of reports for antimalarials and anthelmintics in the study reaffirms the high prevalence of malaria and anthelmintic infestations in the region and as expected, majority of fatalities observed resulted from antimalarials. However, pyrimethamine/sulfadoxine, which is recommended for intermittent preventive treatment of malaria in pregnancy, was associated with death of three male patients. This observation showed that medicines may be taken by patients for wrong indications. A high number of foetal deaths following artesunate administration were recorded in this study. This observation has not been reported in the literature and further investigations are recommended to determine the true relationship of the drug and events.

CHAPTER SIX

ADVERSE DRUG REACTIONS IN GHANAIAN CHILDREN

6.1 INTRODUCTION

The ADRs for the Ghana adult population have been described in chapter 5. The population of children 0 – 17 years in Ghana is estimated as 11 million [271]. In this population, communicable diseases and perinatal conditions account for 68% of deaths among children under 14 years old [282], and for children under five years of age, malaria is the leading cause of death (Table 6.1) [349].

Table 6. 1: Major causes of death in children under 5 years [349]

Causes of death	Percentage (%)
Malaria	20
Prematurity	14
Acute lower respiratory infections	13
Other causes	13
Birth asphyxia	12
Diarrhoea	8
Neonatal sepsis	7
Congenital anomalies	6
Injuries	5
Measles	1
HIV/AIDS	1

Treatment guidelines for these disease conditions are not properly implemented by healthcare providers in the country [301], and as a consequence, patients may develop ADRs [350].

Reports of paediatric ADR studies in Ghana are limited. However, the safety of pentavalent vaccine in children has been monitored [311]. Ghana is located in Sub-Saharan Africa where malaria is endemic. As part of an effort to reduce the impact of the disease in the region and elsewhere, the World Health Organisation (WHO) recommended a Global Malaria Programme – intermittent preventive treatment in infants (IPTi) – in 2009 [351]. The programme was endorsed by the Expanded Programme on Immunisation (EPI) and the United Nations Children’s Fund (UNICEF) for implementation in addition with routine immunisations in regions with moderate and high malaria burden [352]. Sulfadoxine-pyrimethamine is used in Ghana for the recommended IPTi due to its several advantages over other antimalarials, which includes good efficacy [314], low cost [353], single-dose administration, and no interaction with immunisations [354, 355]. Another major study in Ghana which involved children was conducted to monitor the safety of Sulfadoxine-pyrimethamine – IPTi during routine immunisation [356].

The drugs used in Ghana are not the same as those marketed in other countries, and therefore the ADRs experienced by children will be different. Ghana was the first country in West Africa to join the WHO International Drug Monitoring Programme in 2001, and maintain an ADR database. The national pharmacovigilance centre receives ADR reports for children and forward to UMC where they are entered into VigiBase. No study has been conducted on the Ghana pharmacovigilance database to review the ADRs reported for children. The aim of this study was to describe the type, frequency and

severity of children ADRs and associated drugs in the Ghana pharmacovigilance database.

6.1.1 Aim

To perform descriptive analyses of Ghanaian children ADR reports in VigiBase of UMC.

6.1.2 Objectives

The main objectives of this research are as stated in Chapter 5 (Section 5.1.8).

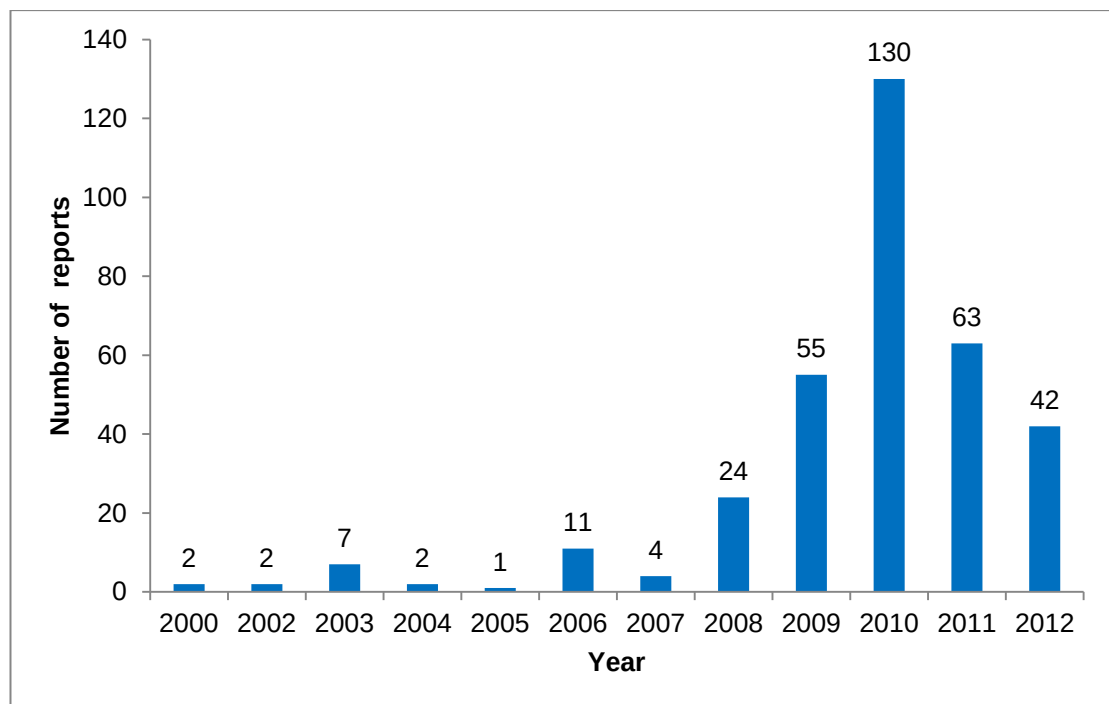
6.2 METHODS

Adverse drug reactions are reported using the form provided by Ghana Food and Drugs Authority. These forms are distributed to all health facilities, regional hospitals, clinics and private hospitals in all the 10 regions in Ghana. The processes of ADR data collection, transmission of reports, report processing, approval for use of the data, data extraction, and method of analysis has previously been described in chapter 3.

6.3 RESULTS

6.3.1 Number of reports

During the 14-year period, 343 reports containing 601 ADRs were received for 343 children from a total of 1819 reports submitted to UMC. This represented an average reporting rate of 2.2 reports per million children per year, and an average of 1.7 ADRs per report. There were no reports received in 1999 and 2001. In the year 2000, and between 2002 and 2007, the number ranged from one to eleven, thereafter, the number rose steadily from 24 in 2008 to a peak of 130 reports in 2010 (Figure 6.1).



Note: Not all the reports received in 2012 were entered into Vigibase when the data was extracted for this study

Figure 6. 1: Number of reports by year

6.3.2 Age group and sex

In the reports where sex was indicated, females made up 164 (48%) of the reports, and males 167 (49%). The proportion of reports where sex was not indicated was 12 (3%). The distribution of reports according to age groups is as shown in Table 6.2.

Table 6. 2: Age distribution of reports

Age group	Reports	
	n	%
Neonates ≤ 27 days	5	1
28 days to 23 months	113	33
2 – 11 years	133	39
12 – 17 years	92	27
Total	343	100

6.3.3 Type of reporters

Nurses submitted half (172, 50%) of the reports. A total of 131 (38%) reports were submitted by pharmacists and physicians, and notifiers of reports were not indicated for 38 (11%) of the cases (Figure 6.2).

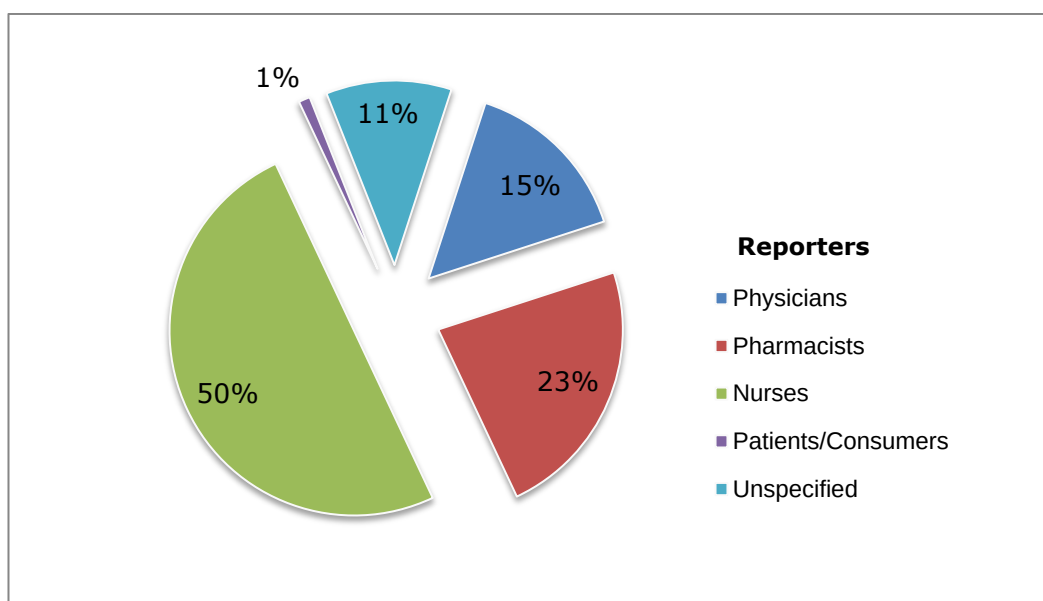


Figure 6. 2: Reporter types

6.3.4 Reported ADRs

The distribution of ADRs according to system organ classification (SOC) is as shown in Table 6.3. ADRs belonging to skin and appendages disorders were most frequently reported, followed by body as whole – general disorders, gastro-intestinal system disorders and application site disorders. Children in age group of 2 – 11 years had more ADRs than those in groups 28 days to 23 months and 12 – 17 years.

Table 6. 3: Distribution of ADRs (SOC) and age groups

Age group/SOC	Neonates ≤ 27 days	28 days to 23 months	2 – 11 years	12 – 17 years	ADR Total	
					n	%
Skin and appendages disorders	0	30	74	44	148	24.6
General disorders	1	54	59	28	142	23.6
Gastrointestinal system disorders	1	28	32	34	95	15.8
Application site disorders	0	63	4	0	67	11.2
Nervous system disorders	0	13	17	26	56	9.3
Psychiatric disorders	1	5	6	5	17	2.8
Respiratory system disorders	1	6	3	4	14	2.3
Vision disorders	0	1	6	5	12	2.0
Urinary system disorders	0	0	6	5	11	1.8
Secondary terms – events	0	4	2	3	9	1.5
Musculoskeletal system disorders	0	0	2	5	7	1.2
White cell and RES disorders	1	3	0	3	7	1.2
Neonatal & infancy disorders	3	0	0	0	3	0.5
Other disorders	0	3	4	6	13	2.2
Total	8	210	215	168	601	100
ADR (% for age groups)	1	35	36	28	100	

Fever, injection site infection and rash were the most frequently reported reactions (Table 6.4). Stevens Johnson syndrome was reported 27 times, representing 4% of the total number of ADRs. There was no dominance for each of the other ADRs reported.

Table 6. 4: Most frequently reported ADRs (preferred terms)

ADR (preferred terms)	n	%
Fever	58	10
Injection site infection	58	10
Rash	34	6
Pruritus	28	4
Vomiting	28	4
Stevens Johnson syndrome	27	4
Abdominal pain	21	4
Asthenia	18	3
Skin reaction localised	17	3
Urticaria	16	3
Rigors	15	2
Diarrhoea	13	2
Convulsions	11	2
Dizziness	11	2
Conjunctivitis	10	2
Others*	236	39
Total	601	100

**ADRs with 9 or less reports were grouped together as others*

6.3.5 Severity of ADRs

Of the total number of 343 reports, 98 (29%) cases were reported with 155 ADRs assessed as serious. 23 children experienced ADRs which led to death. ADRs associated with the criteria of death were more than those that caused life threatening and causing disabling/incapacitating conditions (Table 6.5). Two-thirds of the serious ADRs either caused or prolonged hospitalisation.

Table 6. 5: Severity of ADRs

Severity	Reports (n)
Death	23
Life threatening	12
Caused/prolonged hospitalisation	43
Disabling/incapacitating	8
Other (significant)	2
Unspecified reported severity	10
Total	98

6.3.6 ADR outcomes

Complete recovery of ADR was reported for more than half of the cases (Table 6.6). A total number of 33 ADRs were associated with the 23 deaths. Thirty-five (35) children were recovering from ADRs at the time of report.

Table 6. 6: ADR outcomes for the reports

Outcome	Reports (n)
Died	23
Not recovered	4
Recovered	195
Recovered with sequelae	4
Recovering	35
Unknown	28
Unspecified	70

6.3.7 Suspect drugs

A total of 377 drugs were reported. Some reports had more than one suspect drug, and ADRs associated with these drugs were considered separately. The drug classes most frequently reported were vaccines, antimalarials, antibiotics and anthelmintics (Table 6.7).

Table 6. 7: Drug class and number of reports

Medicine class	Reports (n)	%
Vaccines	115	30.5
Antimalarials	106	28.1
Antibiotics	57	15.1
Anthelmintics	53	14.1
Vitamins	9	2.4
Anti-inflammatory	8	2.1
Anti-epileptics	5	1.3
Immunoglobulins	5	1.3
Analgesics	4	1.0
Antiretrovirals	3	0.8
Anaesthetics	2	0.5
Antihistamines	2	0.5
Herbal products	2	0.5
Antacids	1	0.3
Antifungals	1	0.3
Antipsychotics	1	0.3
Blood products	1	0.3
Mineral supplements	1	0.3
Propulsives	1	0.3
Total	377	100

Anti-infective agents and vaccines made up 19 of the 20 most frequently reported individual suspected drugs (Table 6.8). Of the vaccines, tetanus and

measles vaccines were the most frequently suspected individual vaccines. Amodiaquine/artesunate, amodiaquine and quinine were the most frequently suspected antimalarials. Individual anthelmintic drugs most frequently reported were mebendazole and ivermectin; and ceftriaxone and benzylpenicillin were the most frequently reported antibiotics.

Table 6. 8: Individual drugs and frequency of reports

Drugs	Reports (n)
Tetanus vaccine	56
Measles vaccine	37
Amodiaquine/artesunate	28
Mebendazole	25
Amodiaquine	21
Ivermectin	20
Quinine	19
Pyrimethamine/sulfadoxine	13
Ceftriaxone	10
Artesunate	9
Polio vaccine	9
Albendazole	8
Benzylpenicillin	8
Praziquantel	8
Artemether/lumefantrine	6
Cefuroxime	6
Diclofenac	6
Flucloxacillin	6
Cotrimoxazole	6
Yellow fever vaccine	6
Others	5 and below

6.3.8 Suspect drugs and age groups

Reports were seen more often for children in age group 2 – 11 years than in children aged 28 days to 23 months and 12 – 17 years age groups (Table 6.9). Neonates had the least number of suspect drugs, and vaccines and vitamins were the only suspected classes of drugs. Vaccines were most frequently reported for the 28 days to 23 months children, and antimalarials and antibiotics were reported in almost equal proportion. Reports in children in the age group 2 – 11 years were mostly antimalarials, antibiotics, anthelmintics and vaccines. In the older children, antimalarials, anthelmintics and antibiotics were most often reported.

Table 6. 9: Distribution of drug class number by age groups

Drug class/age group/ number	Neonates ≤ 27 days	28 days to 23 months	2 – 11 years	12 – 17 years	Total (n)
Vaccines	2	90	22	1	115
Antimalarials	0	11	62	33	106
Antibiotics	0	10	27	20	57
Anthelmintics	0	1	24	28	53
Vitamins	3	3	3	0	9
Anti-inflammatory products	0	0	5	3	8
Antiepileptics	0	0	3	2	5
Immunoglobulins	0	0	3	2	5
Analgesics	0	1	3	0	4
Antiretrovirals	0	0	0	3	3
Anaesthetics	0	2	0	0	2
Antihistamines	0	0	0	2	2
Herbal products	0	0	1	1	2
Antacids	0	0	0	1	1
Antifungals	0	0	1	0	1
Antipsychotics	0	0	0	1	1
Blood products	0	0	0	1	1
Mineral supplements	0	0	1	0	1
Propulsives	0	0	0	1	1
Total	5	118	155	99	377

6.3.9 Drug causality assessment for serious ADRs

More than one-third of the ADRs classified as serious were assessed as 'possibly' related to the drugs (Table 6.10). Of the 23 deaths, only one report of a 4 – year old female child who experienced Stevens Johnson syndrome following mebendazole was assessed as 'certainly' related to the drug. The ADRs in the other death reports assessed as 'possible' concerned mainly quinine.

Table 6. 10: Causality assessment for serious ADRs

Assessment	ADRs	
	n	%
Certain	10	6
Possible	58	37
Probable	17	11
Unlikely	11	7
Unknown	3	2
Not assessable	6	4
Not (yet) assessed	1	1
Not specified	49	32
Total	155	100

6.3.10 Deaths reported

Death was reported for 23 (7%) out of the 343 cases analysed, and comprised of 10 males and 13 females. Antimalarials and anthelmintics were reported for the majority of the deaths (Table 6.11). Quinine was associated with 9 (39%) of the death reports and reasons for the deaths were not known. Five deaths were associated with quinine alone, 2 deaths with quinine and ceftriaxone, and one death each for ceftriaxone and chloroquine. Lack of

drug effect with quinine was suspected in the deaths of two female children aged 8 and 9 years.

The death of 5 children was associated with Stevens Johnson syndrome, and these were linked to pyrimethamine/sulfadoxine (2), benzylpenicillin (1), mebendazole (1) and flucloxacillin (1). Two deaths of 4 – year old male children from diarrhoea and hyperpyrexia respectively were reported for ivermectin.

Table 6. 11: Death reports and suspected drugs

Patient	Age	Sex	ADRs	Suspect drugs
1	11 years	F	Stevens Johnson syndrome	Benzylpenicillin
2	9 years	M	Stevens Johnson syndrome	Pyrimethamine/ sulfadoxine
3	10 months	M	Stevens Johnson syndrome	Pyrimethamine/ sulfadoxine
4	12 years	F	Stevens Johnson syndrome	Flucloxacillin
5	4 years	F	Stevens Johnson syndrome	Mebendazole
6	14 years	F	Stevens Johnson syndrome, acute renal failure, sepsis	Albendazole, ivermectin
7	12 years	F	Death*	Quinine
8	14 years	F	Death*	Ceftriaxone, quinine
9	15 years	F	Death*	Quinine
10	3 years	M	Death*	Ceftriaxone, quinine
11	2 years	M	Death*	Quinine
12	13 years	M	Death*	Quinine

**Death was recorded as the ADR in these cases*

Table 6.11: Death reports and suspected drugs continued

13	9 years	M	Death*	Quinine
14	7 years	M	Death*	Ceftriaxone
15	2 years	F	Death*	Chloroquine
16	8 years	F	Medicine ineffective	Quinine
17	9 years	F	Medicine ineffective	Quinine
18	4 years	M	Diarrhoea	Ivermectin
19	4 years	M	Hyperpyrexia	Ivermectin
20	9 years	F	Erythema multiforme	Metronidazole
21	7 months	F	Convulsion, involuntary muscle contraction	Cefuroxime
22	14 months	F	Increased sweating, agitation, vomiting, constipation, dyspnoea	Measles vaccine
23	44 days	M	Injection site bleeding	Tetanus vaccine

*Death was recorded as the ADR in these cases

6.3.11 Critical ADRs

The number of critical ADRs identified were 91, and 72 of these were non-fatal (Table 6.12). Stevens Johnson syndrome, dystonia, face oedema and hyperpyrexia were the most frequently reported critical ADRs. Quinine alone was associated with 8 critical ADRs (hyperpyrexia 7 and decreased hearing 1).

Table 6. 12: WHO-ART critical terms and suspect drugs

Critical ADRs	Number	Suspect drugs
Stevens Johnson syndrome	21	Pyrimethamine/sulfadoxine (4), Cotrimoxazole (2), Ivermectin (2), Albendazole and Ivermectin (1), Ampicillin and Penicillin (1), Phenytoin (1), Bcg vaccine (1), Tetanus vaccine (1), Cloxacillin (1), Measles vaccine (1), Artemether/lumefantrine and Antihistamines (1), Paracetamol, Amoxicillin, Blood products nos and Herbal extracts (1), Flucloxacillin (1), Carbamazepine (1), Vitamins nos (1), Benzylpenicillin (1)
Dystonia	9	Amodiaquine (5), Amodiaquine/artesunate (2), Artesunate (1), Metoclopramide (1)
Face oedema	9	Amodiaquine/artesunate (2), Mebendazole and Praziquantel (2), Amoxicillin (1), Chloramphenicol (1), Pyrimethamine/sulfadoxine (1), Artemether/lumefantrine (1), Immunoglobulin antivenom (1)
Hyperpyrexia	8	Quinine (7), Albendazole and Ivermectin (1)
Mouth oedema	4	Benzylpenicillin and Artemether/lumefantrine (1), Cefaclor (1), Pyrimethamine/sulfadoxine (1), Cotrimoxazole (1)
Dyskinesia	3	Amodiaquine/artesunate (2), Amodiaquine (1)
Neonatal jaundice	3	Menadione (3)
Anaphylactic reaction	2	Mebendazole and Praziquantel (2)
Erythema multiforme	2	Flucloxacillin (1), Pyrimethamine/sulfalene (1)
Generalised oedema	2	Clindamycin (1), Vitamins nos (1)
Paralysis flaccid	2	Tetanus vaccine/Diphtheria vaccine/Hepatitis b vaccine (1), Polio vaccine (1)
Anaphylactic shock	1	Benzylpenicillin (1)
Haematemesis	1	Polio vaccine (1)
Haemolysis	1	Dapsone/chlorproguanil hydrochloride (1)
Decreased hearing	1	Quinine (1)
Hyperkinesia	1	Carbamazepine (1)
Peripheral ischaemia	1	Ceftriaxone (1)
Skin exfoliation	1	Griseofulvin (1)

6.4 DISCUSSION

6.4.1 ADR reports by year and patients

The number of children reports was generally low especially during the first eight years of the study period. This observation is not peculiar to Ghana as underreporting has been acknowledged as a major challenge in pharmacovigilance practice [196]. However, more reports were received, in spite of Ghana's smaller size and population, compared to the previous chapter on Nigeria. This may be attributed to the longer period of time Ghana had been reporting ADRs.

The ADR reporting rate of 2.2 reports per million children per year recorded in this study was not unexpected. This is largely due to the lack of awareness of the importance of reporting ADRs by health professionals [357, 358]. However, with the establishment of the centre of WHO Programme for International Drug Monitoring (UMC – Africa) in Ghana in 2009 [318], awareness in pharmacovigilance has improved. The National Centre for Pharmacovigilance has also been active in its advocacy activities leading to increased reporting over the years, though the fall in reports between 2011 and 2012 is of concern.

A large proportion of reports in this study concerned children aged 2 – 11 years, which was similar to the observation in the Nigerian children report in Chapter 4. This observation has also been reported in a study conducted in Spain [107]. However, it was in contrast with the report from Denmark where majority of cases reported were for infants aged 0 – 2 years [79].

6.4.2 Notifiers of ADRs

Nurses submitted more than half of the reports. The high number of nurses' reports observed may be attributed to their involvement in active monitoring of swine flu (H1N1) pandemic vaccination in Ghana [359], and unique role in observing patients' early signs and symptoms of drug reactions [118]. This was in contrast with the Nigerian children reports, and other similar studies conducted in Canada and Netherlands, where pharmacists submitted more ADRs as patients consult with them directly at pharmacy outlets [30, 108]. However, physicians have reported more ADRs than other healthcare professionals including nurses and pharmacists in Spain [107], but in India, physicians knowledge of pharmacovigilance have been reported as inadequate [360]. The key to success in adverse drug reaction reporting rest on adequate education for healthcare professionals which has been adopted in Cuba, and reporting rate has improved [113].

6.4.3 ADRs and drug class

Skin and appendages disorders which included rash, pruritus and Stevens Johnson syndrome were most frequently reported in this study. This observation was similar to the Nigerian children study, and the paediatric studies reviewed which were conducted in Spain [81] and China [114]. Vaccines constituted the highest number of drugs reported. This observation was consistent with majority of the European paediatric studies reviewed in Chapter 2, and contrasted with the Nigerian study and the studies reviewed in USA, where antiretrovirals, mostly from perinatal exposure, and medicines used to treat paediatric attention deficit hyperactivity disorder (ADHD) were

respectively the most frequently reported drugs. The large number of antiretroviral reports in the Nigerian study may be attributed to the encouragement given to healthcare professionals to report all ADRs experienced by HIV/AIDS victims by the NGOs that provide materials and support for sufferers.

Funding for pharmacovigilance activities in developing countries is not encouraging, and available resources are mostly directed to implementing vaccine immunisation programmes, particularly for children [361].

In an analysis of 249 neonatal cases of tetanus in Ghana, an overall mortality rate of 64% was reported [362], and this called for an urgent control of the disease. The pentavalent vaccine was consequently introduced to immunise children in Ghana in 2002, and this was reported to be safe and well tolerated [311]. The immunisation programme implemented to control the disease was reflected in the large number of vaccine reports observed in this study. Children aged between 0 – 2 months were administered the pentavalent vaccine which was largely associated with fever and other injection site reactions. These findings were consistent with previous studies conducted in Sweden and Cuba [80, 113]. A factor which may contribute to the high level of ADRs experienced is the site of immunisation of the vaccines, and the greater risk of local reactions associated with vaccination in the arm for children aged between 1 and 6 years [363]. It is therefore not unexpected for this group of children to experience these reactions as the immunisation programme against the deadly disease, tetanus with pentavalent vaccine, was directed at them.

6.4.4 Death reports

The proportion of fatality (7%) recorded in this study was similar to the Nigerian study, and higher compared with the paediatric studies reviewed in Chapter 2, where the proportion ranged between 0.1 – 2.2% (Europe), and 0.2 – 1.6% (Latin America). However, it is lower than the proportion observed in North America, where the average was 8.0%.

Malaria is a major contributor of child mortality in sub-Saharan Africa, and quinine, which was primarily used for its treatment, was replaced with artesunate-amodiaquine as first line of therapy in Ghana in 2005 [364]. The ADRs for majority of the fatalities were reported as ‘death’ and ‘drug ineffectiveness’ and quinine was associated with these events. There were no fatalities with artesunate or its combination in this children population. These findings were consistent with the results of an open-label randomised clinical trial on children with severe falciparum malaria, in which treatment with artesunate was reportedly superior to quinine, with higher deaths in the quinine group [365]. Quinine is still the choice for malaria therapy in sub-Saharan Africa due to its low cost [366], and effectiveness [367]. Even though quinine has been reported as less effective when compared to artesunate [368], both are in use in Ghana. The choice may depend on availability, cost and preference of the prescriber. The presence of counterfeit and substandard antimalarials, particularly, quinine in sub-Saharan Africa has been recognised [369], particularly, in Ghana [162]. It is possible that the reported fatalities from unknown causes and medicine ineffectiveness in this study may have resulted from counterfeit and substandard quinine use.

Intestinal worm infestation affects between 11 and 12% of children aged 5 to 14 years [370]. This represents the largest contributor to disease burden for this age group, however, there is no accurate estimate on prevalence in Ghana, but anecdotal evidence suggests it is similar to the global situation [370]. Three of the 4 fatalities due to anthelmintics in this study were recorded between 2008 and 2009.

The first nationwide programme to deworm children in Ghana was initiated in 2007. However, the programme was derailed due to bad media publicity on rumours of deaths associated with the drugs used for the programme [371]. It is possible that these deaths may be linked to the programme or that the reporting of these cases was occasioned by the bad publicity.

Anthelmintic drugs should be administered only to individuals who are well. This is because of the possibility that the subject may die of a pre-existing illness, and it could be concluded that the anthelmintic had caused the death [372]. It was not possible to determine in this study if the patients who died following anthelmintics were previously well or had other comorbid conditions.

Two patients who died following ivermectin suffered diarrhoea and hyperpyrexia. In the Nigerian children section of this study, no death was reportedly associated with anthelmintics, even though the prevalence of intestinal worm was high in Nigeria [373].

Stevens Johnson syndrome was linked to the death of a 4-year old female patient following mebendazole in this study, and drug causality assessment

for this association was 'certain'. Reports of this association in the literature is scanty for children, however, it has previously been reported to occur in adults [374, 375].

6.5 CONCLUSION

Vaccines, antimalarials and antibiotics are the leading medicines causing reported ADRs in Ghanaian children. Majority of the reports were submitted by nurses. There was a high mortality rate of 7% among the reports and of the 23 deaths reported, 6 were due to Stevens-Johnsons Syndrome. Some of the children who died were administered antimalarials, and death was reported as the ADR. It may be that these antimalarials are substandard. These observations underscore the importance that should be given by the regulatory authority to curtail the marketing of substandard medicines in the Ghanaian market. However, the Ghana Food and Drugs Authority had on several occasions alerted consumers on the presence of counterfeit and substandard quinine in the Ghanaian medicine supply chain [376], and the authority is regularly monitoring medicinal products used in the country. It is also taking necessary actions in withdrawing identified counterfeit and substandard medicines, and penalising producers and marketers of such identified drugs.

The study also revealed there is underreporting of ADRs for children, considering when Ghana became a member of the International Drug Monitoring Programme in 2001. This could be improved with combined

education and mobilisation of healthcare professionals and consumers by the National Pharmacovigilance Centre and UMC – Africa.

CHAPTER SEVEN

STUDY CONCLUSIONS

7.1 INTRODUCTION

The establishment of the WHO International Drug Monitoring Programme has helped to promote the reporting of ADRs in the two member states [40]. Ghana and Nigeria joined the programme in 2001 and 2004 respectively [377], and have since then been submitting ADR reports to the International ADR database, VigiBase.

Ghana and Nigeria are located in the same tropical zone of sub-Saharan Africa. Both countries have similar healthcare delivery systems, where patients are first treated in their local community health centres before being referred to regional/state and teaching hospitals. Physicians are the cornerstone of healthcare delivery in the two countries, and therefore well placed to observe and report ADRs [182]. However, other healthcare professionals (HCPs) and consumers/patients also submit reports to the NPCs of the two countries.

In Africa, the reporting of ADRs has been enhanced by the establishment of an arm of the Uppsala Monitoring Centre (UMC – Africa) in Ghana. The role of the establishment is to provide support to the NPCs of African member states and training of healthcare professionals in pharmacovigilance [318]. In addition, UMC – Africa provide healthcare professionals with current updates of regulations and guidelines for reporting of ADRs.

The NPC in Ghana and Nigeria receive reports of ADRs in a similar form designed to capture details of reporter, patient, ADR(s) and suspect drug(s) including concomitant medications and medical history of patients. ADRs are evaluated and assessed for causal relationship between drugs and ADRs by committees of experts in pharmacovigilance before they are entered into the national database. Both countries code suspect drugs according to WHO Drug Dictionary Enhanced (WHO-DD) [195], and ADRs were coded based on WHO Adverse Reaction Terminology (WHO-ART) [192]. The ADR database of Ghana and Nigeria therefore contain the same data elements and are the source of new information about the safety of drugs in the 'real-world' setting [319]. They also serve as information source about drugs used in these two countries and the associated ADRs, which could be compared with those from other countries.

This thesis aimed to highlight the status of ADRs for adults and children in Ghana and Nigeria. Even though the healthcare delivery system and the ADR reporting procedures are similar, overview of the general reports of the two countries showed some differences in the pharmacovigilance descriptors contained in the two databases, and when compared with reports of studies conducted in Europe, Asia, North America and Latin America.

7.2 SUMMARY OF FINDINGS

7.2.1 Reports from the literature

The 41 studies reviewed (Chapter 2) involved 20 paediatric and 21 general population studies conducted in Europe (24), North America (5), Asia (5), Latin America (2) and in Africa, only one study was identified. A total of 4 studies were conducted from WHO ADR database, Vigibase. In both the paediatric and general population studies, physicians submitted more reports than other healthcare professionals. It was also observed that ADR reporting rates were higher in countries which have established pharmacovigilance systems. An exceptionally high reporting rate was observed in the two studies conducted in Cuba. This was attributed to special education on pharmacovigilance for healthcare professionals.

In both the general population and paediatric studies identified, skin disorders were the most frequently reported ADRs. In the general population studies, anti-infectives for systemic use and nervous system drugs were most frequently reported. The only study identified in Africa was on the general population, and antiretrovirals were the most frequently reported drugs. Anti-infectives for systemic use, mostly vaccines were the most frequently reported drugs in the European, Latin American and Asian paediatric studies. In the North American paediatric studies, drugs used for treating ADHD were mostly reported.

The proportions of deaths were higher in the studies conducted in North America for the general population and children compared with the studies identified from the other continents.

7.2.2 Nigerian adult reports

There was a gradual increase in the number of reports from 2010 to 2012. A low reporting rate of 7.2 reports per million individuals per year was observed for this group of population.

Consumers submitted 1% of the reports. Recent initiatives to encourage ADR reporting by consumers include the NPC providing a toll-free telephone line for consumers to report ADRs experienced in the course of taking medications [190]. It is a step taken to encourage reporting of ADRs by consumers and patients in the country. However, the impact of this procedure in improving ADR reporting rate in Nigeria is yet to be determined.

Pharmacists submitted the majority of the reports, with physicians and other HCPs submitting almost the same proportion of reports. This may be attributed to pharmacists' involvement as managers of the HIV/AIDS programme, also supported by the high numbers of antiretroviral reports received. The Non-Governmental Organisations supporting the programme instructed the managers, who are mostly pharmacists, to ensure that all reactions associated with antiretroviral treatments were reported [199].

Antiretrovirals, antibiotics and antimalarials were the group of drugs most frequently reported as causing ADRs. The top ten most suspected individual drugs were all antiretrovirals, except cotrimoxazole.

Rash, pruritus, headache and dizziness were the most common ADRs reported.

The fatality rate for the reported population was 2.4%. The most severe ADRs were various skin related reactions, such SJS, epidermal necrolysis

and skin exfoliation. Antimalarials, antibiotics and antiretrovirals were associated with the deaths and the most severe ADRs.

7.2.3 Nigerian paediatric reports

The paediatric reports made up 6% of the total number of reports submitted for Nigeria during the 8-year period. The ADR reporting rate was 0.4 reports per million children per year. Pharmacists submitted more reports than physicians and other HCPs. More serious ADRs were reported by other HCPs.

The classes of drugs commonly reported for the ADRs were antiretrovirals, antibiotics, antimalarials and vaccines. Rash, fever, pruritus and vomiting were the most commonly reported ADRs.

A fatality rate of 7.1% was observed. The majority of the children who died suffered renal failure which was associated to medicines used for treating teething problems. Stevens Johnson syndrome was the second most common fatal ADR. Metamizole (dipyrone), which has been banned in Nigeria, was associated with some of the deaths.

7.2.4 Ghanaian adult reports

A reporting rate of 7.5 reports per million individuals per year was observed for this population during the period. The rate was higher than that of the adult reports from Nigeria. The higher rate may be attributed to the longer period of time that pharmacovigilance practice has been in operation. This may also be occasioned with the presence of UMC-Africa in Accra, whose

mission is to promote the reporting of ADRs in African member states of WHO International Drug Monitoring Programme. The reporting rate in both countries however is much lower than that seen in most other countries in Europe [82, 95], North America [100] and Asia [51] included in my review of the literature in chapter 2.

There were more reports for the age group 18 – 29 years compared to adults aged 50 years and above. Physicians, pharmacists and other HCPs submitted almost equal number of reports. Other healthcare professionals submitted all the reports between 1999 and 2002, and none between 2003 and 2005. More reports were submitted between 2010 and 2011.

The most common class of drugs were antimalarials, anthelmintics, antiretroviral and antibiotics, and the individual most common drugs were albendazole, amodiaquine/artesunate and ivermectin.

In this population, pruritus, headache, dizziness and asthenia were the most common ADRs.

Fatality rate was 1.8% for this adult population. The most common fatal ADR was Stevens Johnson syndrome due to a variety of drugs. There were also several deaths of foetuses due to artesunate.

7.2.5 Ghanaian paediatric reports

The reports for children aged between 0 – 17 years made up 19% of all the cases submitted to the Ghana NPC during the period. This figure represented an average reporting rate of 2.2 reports per million children per year. Half of the reports were submitted by nurses.

Vaccines, antimalarials, antibiotics and anthelmintics were the most frequently reported drugs. The individual most common drugs were tetanus vaccine and measles vaccine, mostly reported by nurses for infants.

Fever, injection site infection, rash and pruritus were the most common ADRs. Serious ADRs were reported for 29% of the children.

6.7% of the reports had a fatal outcome. The majority of the deaths which were linked with anti-infective agents, mostly antimalarials and anthelmintics, resulted from Stevens Johnson syndrome and from other unknown causes.

7.2.6 An overview

An overview of the two datasets revealed more data completeness in the Ghana ADR database compared to Nigeria. This observation may be interpreted to mean that reporters in Ghana were more thorough in completing the required information in the ADR form than their Nigerian counterparts.

There were observed differences in the reported drugs in the two countries. This may be attributed to prevailing disease conditions at the time of reporting the ADRs. The higher number of antiparasitic products (antimalarials and anthelmintics) observed in the Ghana data was an indication of the prevalence of malaria disease [378] and worm infestations [379]. The high proportion of antiretroviral drugs observed in Nigeria may be linked to the high prevalence of HIV/AIDS [129], and to the encouragement of healthcare professionals by sponsors of the HIV/AIDS programme to report

all ADRs experienced by HIV/AIDS victims following antiretroviral therapy [199].

The ADR reporting rates and fatality rates for the populations studied in Nigeria and Ghana are shown in Table 7.1. It was observed that the reporting rates were higher for the Ghanaian studies compared to Nigeria. This indicates that there is more awareness of ADR reporting in Ghana compared to Nigeria. The fatality rates were higher in the Nigerian studies.

Table 7. 1: Reporting rates and fatality rates

Population studied	Reporting rate (reports per million individuals per year)	Fatality rate (%)
Nigerian adults	7.2	2.4
Nigerian children	0.4	7.1
Ghanaian adults	7.5	1.8
Ghanaian children	2.2	6.7

Stevens Johnson syndrome following pyrimethamine/sulfadoxine was associated with fatalities in Ghana and Nigeria. Malaria is endemic in the two countries and pyrimethamine/sulfadoxine is used as prophylaxis in both children and adults.

In the adult reports, patients in Ghana died from SJS due to pyrimethamine-sulfadoxine, acetylsalicylic acid/caffeine and albendazole/ivermectin. Whereas in Nigeria, the majority of the deaths also resulted from SJS with mostly pyrimethamine/sulfadoxine, cotrimoxazole and nevirapine as suspect drugs.

Whereas the cause of death resulting from quinine in majority of Ghanaian children could not be explained, Nigerian children died mostly from renal failure due to suspected contaminated paracetamol/diphenhydramine hydrochloride and herbal products used for teething problems.

The data used for this study were entered into the WHO World-Wide ADR database, Vigibase, after the reports have been processed by the NPCs in Ghana and Nigeria. The pharmacovigilance parameters in this study were described as reported in the database. The assessment of severity of the ADRs and drug causality were made by the reporting HCPs. In the cases where causality assessments were not provided in the reports, a committee meets regularly to assess the relatedness of the ADRs to the drugs and assign an agreed causality. In the majority of the reports, indication for use, start and stop dates, dosage, route of administration, dechallenge and rechallenge dates of the drugs were not provided. The lack of causality assessment for the majority of the reports may be due to this missing information in the report forms submitted by the HCPs. Some of the ADRs were reported as serious without severity criteria, and outcome of most ADRs were not provided. Lack of this information made it impossible to determine the true ADR status of the two countries. Therefore more work need to be done in the area of training of HCPs in pharmacovigilance practice. Generally, the data do not provide a true reflection of the amount and type of drugs that are in use in Ghana and Nigeria.

7.2.7 Implications of the study

Paediatric safety data are generally not available due to limitations of involving children in clinical trials. Therefore spontaneous reporting is the source from which data is obtained to assess the risk-benefit of drugs in the paediatric population.

Different classes of drugs were responsible for the paediatric fatalities in the two countries. In Ghana, several deaths due to unknown causes were reportedly associated with the antimalarial, quinine. Underlying disease conditions may be attributed to these deaths. However, this cannot be confirmed from the data as it doesn't contain information of medical history of the children. The deaths may also be attributed to the quality of the antimalarials. The presence of substandard antimalarials in the supply chain in Ghana has been identified, and the health authority in the country needs to put adequate measures in place to curb the sale of these products.

The deaths in the paediatric population in Nigeria were mostly associated with paracetamol diphenhydramine hydrochloride and herbal medicines. The paracetamol diphenhydramine hydrochloride administered to the children was discovered to be contaminated with diethylene glycol by the health authorities. The company which produced these medicines was identified, and the management was prosecuted and found guilty of not implementing good manufacturing practices. They were consequently jailed as a deterrent to others. The herbal products associated with the fatalities were used for treating teething problems. These findings underscore the need for the health authorities to enforce enabling guidelines for production of high quality herbal medicines for children.

7.3 Limitations

Pharmacovigilance is still in its infancy in Ghana and Nigeria. As a result of this, most data elements were missing from the ADR databases of the two countries. Therefore, it was not possible to evaluate all the pharmacovigilance descriptors in this study for the two countries.

Even though reports in national ADR databases reflect both real-life events and drug use, the reports in the databases have not provided the true ADR status of the two countries. For instance, ADR reports submitted to the NPCs on the pharmacovigilance of particular drugs could provide misleading information about the associated ADRs when all the reports are aggregated, as seen in the case of antiretroviral reports in Nigeria.

The ADR databases also lacked information on drug exposure and utilisation in the population. In addition, there is no indication in the database of the region or state from where the reports originated. The presence of this information would have helped the health authorities to manage and provide support for the patients. A significant limitation to the study was lack of explanation on the reason why certain important information were reported or not provided in the databases.

The HCPs provide the assessment of severity of the ADRs. The UMC however used a critical ADR classification. Some of the ADRs classified as critical were not reported as serious, and there was significant overlap between these two classification systems. The number of critical ADRs was greater than the number of serious ADRs for both Ghana and Nigeria. A uniform method of identifying serious/critical ADRs would be helpful.

7.4 Further studies

The outcomes of this study necessitate a recommendation for conducting further studies in the areas required to improve reporting rates and quality of data, and drug utilisation in both countries. The following studies are therefore suggested:

- Assessment of healthcare professionals' awareness in pharmacovigilance. The assessment of knowledge of pharmacovigilance among healthcare professionals will enable the authorities to initiate and provide educational programmes that will highlight the importance of ADR reporting in healthcare delivery. The outcome of such programmes will improve reporting rates, and quality of data submitted to the PV centres.
- Determination of limiting factors of ADR reporting in local PV units. Knowledge gained from these studies will enable the authorities to ensure the provision of resources required by healthcare professionals to effectively report ADRs.
- Evaluate consumer telephone reporting of ADRs in Nigeria. Data generated from this study will enable the authorities to further develop and improve on the reporting system.
- Assessment of drug utilisation. This study will be carried out to determine the types of drugs prescribed to consumers in a given locality. Data generated from these studies can be used as reference to the types of drugs reported for ADRs in PV databases.

7.5 Conclusions

National ADR databases are important resource for information on drug safety in the population, especially for children, women and the elderly who are often not included in drug clinical trials.

Adverse drug reactions from National ADR database of high- and medium-income countries have been described and reported. Only one study has been conducted from a National ADR database in Africa. Drugs reported for the ADRs in the general population in all the continents were mostly anti-infectives. In children, vaccines were mostly reported in Europe, Asia and Latin America, and drugs used for ADHD were common in North America. In the two populations, death rates were higher in North America than in Europe, Asia and Latin America.

ADR reporting rates were low in Ghana and Nigeria. This implies the reporting systems in the two countries need improvement.

The most frequently reported ADRs for children and adults in Ghana and Nigeria were skin disorders. These were largely associated with anti-malarial drugs and anthelmintics in Ghana. In Nigeria, they were mostly associated with antiretroviral medications.

The fatality rates were similar for Ghana and Nigeria. In the adults, it was 1.8% for Ghana and 2.4% for Nigeria. In the children, it was 6.7% for Ghana and 7.1% for Nigeria.

The fatalities for Nigerian adults were mainly associated with antiretroviral medications.

A larger proportion of children who died in the Nigerian reports suffered renal failure arising from suspected contaminated medicines and herbal products for treating teething problems.

Antimalarials and anthelmintics were the most implicated medications in the fatalities reported for adults and children in Ghana.

In the adult population in Ghana and Nigeria, Stevens Johnson syndrome and pyrimethamine/sulfadoxine was the most common pair of ADR and drug associated with the fatalities.

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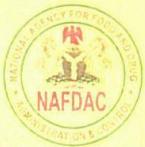
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APPENDICES

Appendix 1: NAFDAC, Nigeria ADR Form

NATIONAL PHARMACOVIGILANCE CENTRE (NPC) NIGERIA					
National Agency for Food and Drug Administration & Control (NAFDAC), Headquarters Office Plot 2032 Olusegun Obasanjo Way Wuse Zone 7 Abuja			 FORM FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS IN STRICT CONFIDENCE Tel: 08086899571 or 07093211221		
1. * PATIENT'S DETAILS					
Full Name or Initials: _____			Patient Record No: _____		
AGE/DATE OF BIRTH: _____			SEX: M ☐ F ☐ WEIGHT (kg): _____		
HOSPITAL/Treatment Centre: _____					
2. * ADVERSE DRUG REACTION (ADR)					
A. DESCRIPTION		C. OUTCOME OF REACTION TICK AS APPROPRIATE ☐ Recovered fully ☐ Recovered with disability (Specify) _____ ☐ Congenital Abnormality (Specify) _____ ☐ Life Threatening (Specify) _____ ☐ Death ☐ Others (specify) _____			
DATE Reaction Started		DATE Reaction Stopped			
B. Was Patient Admitted Due to ADR Yes ☐ No ☐					
If Already Hospitalized, Was it Prolonged Due to ADR Yes ☐ No ☐					
Duration of Admission (days) _____					
Treatment of Reaction: _____					
3. * SUSPECTED DRUG (Including Biologicals Traditional/Herbal Medicines & Cosmetics)					
A. DRUG DETAILS (State name and other details if available / attach product label / Sample (if available))					
Brand Name: _____		Generic Name: _____		Batch No: _____	
NAFDAC No: _____		Expiry Date: _____			
Name & Address of Manufacturer: _____					
B. Indications for Use	Dosage	Route of Administration	Date Started	Date Stopped	
4. * CONCOMITANT MEDICINES (All medicines taken within the last 3 months including herbal and self medication)					
Brand or Generic Name	Dosage	Route	Date Started	Date Stopped	Reason for Use
5. * SOURCE OF REPORT:					
Name of Reporter: _____					
Address: _____					
Profession: _____					
Signature: _____		Date: _____		Tel No/E-mail: _____	
* : MANDATORY FIELDS					

FORMS ARE AVAILABLE AT www.nafdac.gov.ng AND CAN BE SENT TO npcadr@nafdac.gov.ng

Appendix 2: Application for use of Nigeria data

The Director-General

National Agency for Food and Drug Administration & Control (NAFDAC)

Plot 2032 Olusegun Obasanjo Way, Wuse, Zone 7 ABUJA, NIGERIA

14 December 2011

Dear Dr Orhii,

USE OF NAFDAC PHARMACOVIGILANCE DATA

I hereby apply formally for permission/approval to be granted for me to access the NAFDAC Pharmacovigilance database for research purposes towards my PhD in Paediatric Clinical Pharmacology at the UCL Institute of Child Health, London, under Nigerian Government (PTDF) Scholarship.

The research will aim at characterising the various adverse drug reactions reported against the medications used by patients of all groups including children. The severity of the drug reactions will also be examined in this research. Also, the drug products that are most commonly reported to have caused the adverse events will be determined. The outcome of this research will give NAFDAC the pointer to suspected fake drug products, and thus effectively direct resources to fight the fake drug menace in the country and get rid of them.

Thank you for the anticipated and kind approval.

Yours sincerely,

Kennedy Cliff-Eribo & my Supervisor

Appendix 3: Approval letter for use of Nigerian PV data from NAFDAC

From: nafdac Abuja [<mailto:nafdacprs@yahoo.com>]

Sent: 27 January 2012 11:16

To: Sutcliffe, Alastair <a.sutcliffe@ucl.ac.uk>

Subject: Re: Use of NAFDAC PV data

Dear Kennedy,

The Planning Research & Statistics (PR&S) Directorate of NAFDAC wishes to convey to you the DG's approval of your request to use the Nigerian PV data domiciled in NAFDAC for academic reasons. To this effect you are to contact the National Coordinator of PV in Nigeria – Pharm. (Mrs.) A. I. Osakwe via the email address below:

pharmacovigilance@nafdac.gov.ng AND/OR nafdac_npc@yahoo.com

Kindly restate to her in specific terms the particular data/information you require as well as the possible format in which you want them.

Please also refer all other questions/enquiries on PV in Nigeria to the Coordinator above.

Thank you.

Pharm. F. M Tatama

DD, PR&S

Appendix 4: Ghana Food and Drug Authority ADR data Form

GHANA – ADR REPORTING FORM

FDA/SMC/SMD/GL-RAR/2013/01

(A) DETAILS OF PATIENT

Age/Date of Birth (dd/mm/yyyy): / / Gender: M () F () Wt: kg
 Name/Folder Number.....Telephone No.....
 Hospital/Treatment Centre.....

(B) DETAILS OF ADVERSE REACTION AND ANY TREATMENT GIVEN (Attach a separate sheet when necessary)

Date reaction started (dd/mm/yyyy): / / Date reaction stopped (dd/mm/yyyy): / /

(C) OUTCOME OF ADVERSE REACTION:

Recovered () Not yet recovered () Unknown ()

Did the adverse reaction result in any untoward medical condition? Yes () No () If yes,
 Specify

SEVERITY: Death () Life threatening () Disability () (specify).....Hospitalization ()

Others (specify).....

(D) SUSPECTED PRODUCT(S) (Attach sample or product label if available)

Brand name	Generic name	Batch no.	Expiry date	Manufacturer
Reasons for use (indication)	Daily dose	Route of Administration		
Date started:		Date stopped:		
Did the adverse reaction subside when the drug was stopped (de-challenged)? Yes () No ()				
Was the product prescribed? Yes () No ()		Source of Drug:		

Was product re-used after detection of adverse reaction (re-challenge)? Yes () No ()

Did adverse reaction re-appear upon re-use? Yes () No ()

(E) CONCOMITANT DRUGS INCLUDING HERBAL MEDICINES TAKEN PRIOR TO THE ADVERSE REACTION

(Attach a separate sheet when necessary)

Name of Drug	Daily dose	Date started	Date stopped	Reasons for use

Attach all relevant laboratory tests/data

(F) DETAILS OF REPORTER

Name of Reporter:
 Address:
 Profession:
 Signature:
 Tel:
 E-mail:
 Date (dd/mm/yyyy):

Appendix 5: Application for use of Ghana Food and Drugs Authority ADR data

fdb@fdbghana.gov.gh

The CEO

Ghana Food and Drugs Board

National Pharmacovigilance Centre

Accra, Ghana

20 July 2012

Dear Sir/Madam,

USE OF GHANA PHARMACOVIGILANCE DATA

I hereby apply for permission/approval to be granted for me to access the Ghana Pharmacovigilance database for research purposes towards my PhD in Paediatric Clinical Pharmacology at the University College London Institute of Child Health, London.

The research will aim at characterising the various adverse drug reactions reported against the medications used by patients of all groups including children. The adverse events reported in association with the respective drugs will also be examined in this research. Also, the drug products that are most commonly reported to have caused the adverse events will be determined.

The outcome of this research will be documented in the literature, and the National Pharmacovigilance Centre of Ghana Food and Drugs Board will duly be acknowledged.

Thank you for the anticipated and kind approval.

Yours sincerely,

Kennedy Cliff-Eribo & my Supervisor

Appendix 6: Approval for use of Ghana PV data

-----Original Message-----

From: FDB Mail [<mailto:fdb@fdbghana.gov.gh>]

Sent: den 31 oktober 2012 18:00

To: ADRinfo; Kristina Star <Kristina.Star@who-umc.org>

Cc: k.cliff-eribo.11@ucl.ac.uk

Subject: USE OF GHANA PV DATA

Dear Anita & Kristina,

This is with respect to the request from Kennedy Cliff- Eribo to use the Ghana ADR data in support of research being undertaken at the UCL Institute of Child Health, UCL London as part of his PhD programme.

The Food and Drugs Board, Ghana, gives permission for this data to be extracted for this purpose only on condition that we can be assured that no confidential patient information will be disclosed.

Kindly acknowledge receipt of this email indicating your acceptance of the above conditions.

Thank you

Delese Darko

Head; Safety Monitoring Dept

For: Chief Executive

Appendix 7: Data elements for each report extracted for the study

CountryText	SafetyReportId	CompanyNumb	Serious	Seriousness	Died
ReportTypeCode	ReportType	NotifierTypeCode	NotifierType	AgeReaction	AgeU
AgeUnit	GenderCode	Gender	datebirth	ReOutcome	OnsetDate
MedProd_ID	ReportedDrug	MAH	MAHolder	PreferredBase	PreferredBaseName
PreferredSalt	PreferredSaltName	BasisCode	Basis	StartDate	StopDate
Amount	AmountCode	AmountUnit	Frequency	FrequencyCode	FrequencyUnit
RouteCode	Route	IndicationSupText	IndicationText	ReportedTermOriginal	ReportedTerm
ReactionSerious	ReactionSeriousness	WhoArtSocCode	WhoArtArecno	WhoArtSeq	
WhoArtSOC_name	WhoArtPT_name	WhoArtLLT_name	CausalityCode	Causality	
Dechallenge1	DechallengeAction	Dechallenge2	DechallengeOutcome		
Rechallenge1	RechallengeAction	Rechallenge2	RechallengeOutcome		

Appendix 8: Critical ADRs

Abortion	Cognitive disorders	Haemolysis	Lower motor neurone lesion
Acidosis lactic	Coma	Haemolytic-uraemic syndrome	Manic reaction
Aggressive reaction	Convulsions grand mal	Haemoptysis	Melaena
Amnesia	Corneal ulceration	Haemorrhage in pregnancy	Myopathy
Anaemic aplastic	Deafness	Hallucination	Narcolepsy
Anaemic haemolytic	Death	Hearing decreased	Nephrophathy toxic
Anaphylactic reaction	Death foetal	Hemiplegia	Neuritis
Anaphylactic shock	Delirium	Hepatic cirrhosis	Neuropathy
Aneurysm	Delusion	Hepatitis	Neuropathy peripheral
Angioedema	Dementia	Hepatocellular damage	Oedema generalised
Anorexia nervosa	Dermatitis exfoliative	Hyperkinesia	Oedema mouth
Anuria	Diabetes mellitus	Hyperpyrexia	Oesophageal ulceration haemorrhagic
Apnoea	Diarrhoea bloody	Hypertonia	Ototoxicity
Arrhythmia	Dyskinesia	Hypoglycaemia	Pancreatitis
Asphyxia	Dystonia	Hypothermia	Paralysis flaccid
Asthma	Epidermal necrolysis	Immune system disorder	Paraplegia
Blindness	Epistaxis	Infection TBC	Peptic ulcer
Bronchospasm	Erythema multiforme	Intestinal ulceration	Peripheral gangrene
Cachexia	Face oedema	Jaundice haemolytic	Peripheral ischaemia
Cardiac arrest	Foetal distress	Jaundice neonatal	Phlebitis
Cardiac failure	Gastric dilatation	Keratoconjunctivitis	Photosensitivity reaction
Cardiomyopathy	Gastric ulcer	Laryngismus	Polyuria
Cerebral haemorrhage	GI haemorrhage	Larynx oedema	Porphyria
Circulatory failure	Glaucoma	LE rash	Post-menopausal bleeding

Appendix 8: Critical ADRs continued

Coagulation factor decreased	Haematemesis	Linear IgA bullous dermatosis	Psychosis
Psychosis manic-depressive	Respiratory distress syndrome	Spasm generalised	Vasculitis
Purpura	Schizophrenic reaction	Stephens Johnson syndrome	Vestibular disorder
Renal failure acute	Sepsis	Sudden death	Visual field defect
Renal failure chronic	Skin exfoliation	Tetany	
Renal function abnormal	Skin necrosis	Thrombocytopenia	
Respiratory depression neonatal	Skin ulceration	Uterine haemorrhage	

PUBLICATIONS

PAPERS

1. **Cliff-Eribo KO**, Sammons H, Star K, Edwards IR, Osakwe A, Choonara I. Adverse Drug Reactions in Nigerian Children - A Retrospective Review of reports submitted to the Nigerian Pharmacovigilance Centre from 2005 to 2012. Paediatr Int Child Health. 2015 Sep 8:2046905515Y0000000059.

2. **Cliff-Eribo KO**, Choonara I, Dodoo A, Darko D, Sammons H. Adverse Drug Reactions in Ghanaian Children - Review of reports from 2000 to 2012 in VigiBase. Expert Opin Drug Saf. 2015 Oct 5:1-7.

ABSTRACT

Cliff-Eribo KO, Choonara I, Sammons H. Adverse Drug Reactions in Nigerian Children. *Arch Dis Child* 2014; 99: A124 doi:10.1136/archdischild-2014-306237.285

ADC G302 Adverse Drug Reactions in Nigerian Children

K Cliff-Eribo, I Choonara and H Sammons

Arch Dis Child 2014 99: A124