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Global patterns of adverse drug reactions related to doxorubicin, epirubicin and methotrexate: analysis of individual case safety reports in Vigibase

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GLOBAL PATTERNS OF ADVERSE DRUG REACTIONS RELATED TO DOXORUBICIN, EPIRUBICIN AND METHOTREXATE: ANALYSIS OF INDIVIDUAL CASE SAFETY REPORTS IN VIGIBASE

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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Pharmacy

Johannesburg, 2022

Declaration

I, Deborah Anuoluwapo Matesun, declare that this dissertation submitted to University of the Witwatersrand for the degree of Master of Pharmacy has not previously been submitted for any degree or examination at any other University. This dissertation is my own unaided work, except for cases in which the work of others has been cited and duly acknowledged within the context of the dissertation.



23rd June, 2022

Deborah A. Matesun Date

Dedication

This dissertation is dedicated to Almighty God and my late beloved father, Engineer Titus Olurogba Oloidi, who would have expected nothing less and raised me to always strive to be the best version of myself.

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A special thanks to God Almighty for making this work possible. I am immensely grateful for the strength and enablement to start and complete this research.

To my husband, my pillar, my love, my best friend, I am grateful for the gift of you. Your unwavering support and “never say never” attitude kept me going even when I was unsure of myself. I am grateful. And for the gifts when certain milestones were attained, thank you so much.

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Abstract

Introduction: Cancer is one of the leading causes of death, globally. Chemotherapy drugs are revolutionary in the treatment of cancer. However, their use is associated with a high incidence of adverse drug reactions (ADRs) due to the intrinsic toxicity of the drugs. Pharmacovigilance is essential in oncology as it plays a significant role in evaluating the safety of drugs and protecting patients from potentially harmful effects of medicines. This study aimed to analyze the global patterns of ADRs associated with commonly used chemotherapy drugs, doxorubicin, epirubicin, and methotrexate reported to VigiBase, the World Health Organization ADR database.

Method: A quantitative secondary analysis was conducted on ADR reports in VigiBase. A total of 184,318 anonymized individual case safety reports were extracted from VigiBase into spreadsheets on Microsoft Excel. Only reports for doxorubicin, epirubicin, and methotrexate as "suspect" or "interacting" drugs were included in the study. Descriptive statistics were conducted in Microsoft Excel, and data were summarized using frequencies and percentages. Pearson chi-squared test was done to establish associations between ADRs and demographic factors (significance level of $p<0.05$), while binary logistic regression analysis determined the magnitude of association using Stata software.

Results: Blood and lymphatic, general and administration site, and gastrointestinal disorders were commonly reported ADR categories for doxorubicin and epirubicin, while general and administration site condition was the most predominant category for methotrexate. The likelihood of having a therapeutic product effect incomplete was 29% higher in males (OR:1.29 95% CI: 1.16-1.42) and 17% higher in the age group 45-64 years (OR:1.17, 95% CI: 1.06-1.29). Also, children (ages 2-11 years) showed 3.33 times higher odds of developing pyrexia (OR:3.33, 95% CI: 1.55-7.18). A comparison between the ADRs found on the drug package inserts in South Africa and the VigiBase data revealed that certain ADRs were not labeled on the package inserts. The main findings were off-label use, disease progression, constipation, decreased appetite, pulmonary embolism, pain, pneumonia, nervous system disorders, and drug therapy issues.

Conclusion: This study contributes to the knowledge of ADRs associated with commonly used chemotherapy drugs. It can assist in minimizing ADR risks and enhancing cancer patient safety.

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List of Abbreviations

ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
AE	Adverse Event
ME	Medication Error
SE	Side Effect
WHO	World Health Organization
PMS	Post Marketing Surveillance
PV	Pharmacovigilance
PIDM	Programme for International Drug Monitoring
CEM	Cohort Event Monitoring
UMC	Uppsala Monitoring Centre
ICSR	Individual Case Safety Report
ICH	International Conference on Harmonization
SAHPRA	South African Health Products Regulatory Authority
NADEMC	National Adverse Drug Event Monitoring Centre
MCC	Medicines Control Council
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
HC	Health Canada
EU	European Union
EMA	European Medicines Agency
USA	United States of America
UK	United Kingdom
USD	United States Dollar
PRAC	Pharmacovigilance Risk Assessment Committee

TGA	Therapeutic Goods Administration
HPRA	Health Products Regulatory Authority
MFDS	Ministry of Food and Drug Safety
KIDS	Korean Institute of Drug Safety and Risk Management
PSUR	Periodic Safety Update Report
NDoH	National Department of Health
MHRA	Medicines and Healthcare Products Regulatory Agency
NPC	National Pharmacovigilance Centre
PTC	Pharmacy and Therapeutics Committee
SOC	System Organ Class
PT	Preferred Term
PI	Package Insert
OR	Odds Ratio
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
Dox	Doxorubicin
Epi	Epirubicin
Met	Methotrexate
NHS	National Health Service
MDI	Medical Device Incident
ADRAC	Adverse Drug Reactions Advisory Committee
PCP	*Pneumocystis jirovecii* pneumonia

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

The chapter provides an extensive background for the study**.** It provides an overview of published literature on the aim of pharmacovigilance, adverse drug reactions and their classification, the burden of global adverse drug reactions on the healthcare system as well as global and South African pharmacovigilance systems. Furthermore, a brief discussion of the disease process of cancer and a discussion of the specific drugs and their expected adverse reactions are presented. A summary of the role of pharmacovigilance in oncology and the literature regarding the under-reporting of adverse drug reactions are also provided. Lastly, the rationale of the study, the aim and objectives, and the significance of the study are discussed.

1.2 Definition and Aim of Pharmacovigilance

Adverse drug reactions (ADRs) are a major public health concern, contributing to morbidity and mortality worldwide (Pirmohamed *et al*., 2004). Adverse drug reactions can be damaging, particularly when they are not discovered in time. Clinical trials for a new drug identify a range of ADRs. However, the safety information provided is limited because some ADRs only manifest after drug use in larger populations and over an extended duration (Martin *et al.*, 2004). Therefore, post-marketing surveillance (PMS) is an essential aspect of pharmacovigilance (PV) which monitors the safety of drugs after market approval and allows the detection of rare and population-specific ADRs.

Pharmacovigilance (PV), also known as drug safety, is a tool for monitoring the safety of medicines. The World Health Organization (WHO) defines pharmacovigilance as “the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems” (WHO, 2002a, p.7). Pharmacovigilance-related activities encompass reporting and managing safety data, evaluating individual case safety reports (ICSRs) to detect new signals of ADRs, proactive risk management, and communicating with stakeholders about any potential harm (Fornasier *et al.*, 2018).

The aims of PV, according to the WHO (2002a, p.8) include:

- improving patient care and safety regarding the use of medicines and all medical and paramedical interventions
- rapid detection of problems related to the use of medicine and prompt communication of the findings
- evaluating the effectiveness, harm, benefits, and risks associated with medicines to reduce harm and maximize benefits
- promoting rational, safe, and effective medicine use
- promoting public understanding, education, and clinical training in PV and its effective communication

Over the years, the scope of PV has grown remarkably and is now considered to include the following areas as shown in figure 1.1.

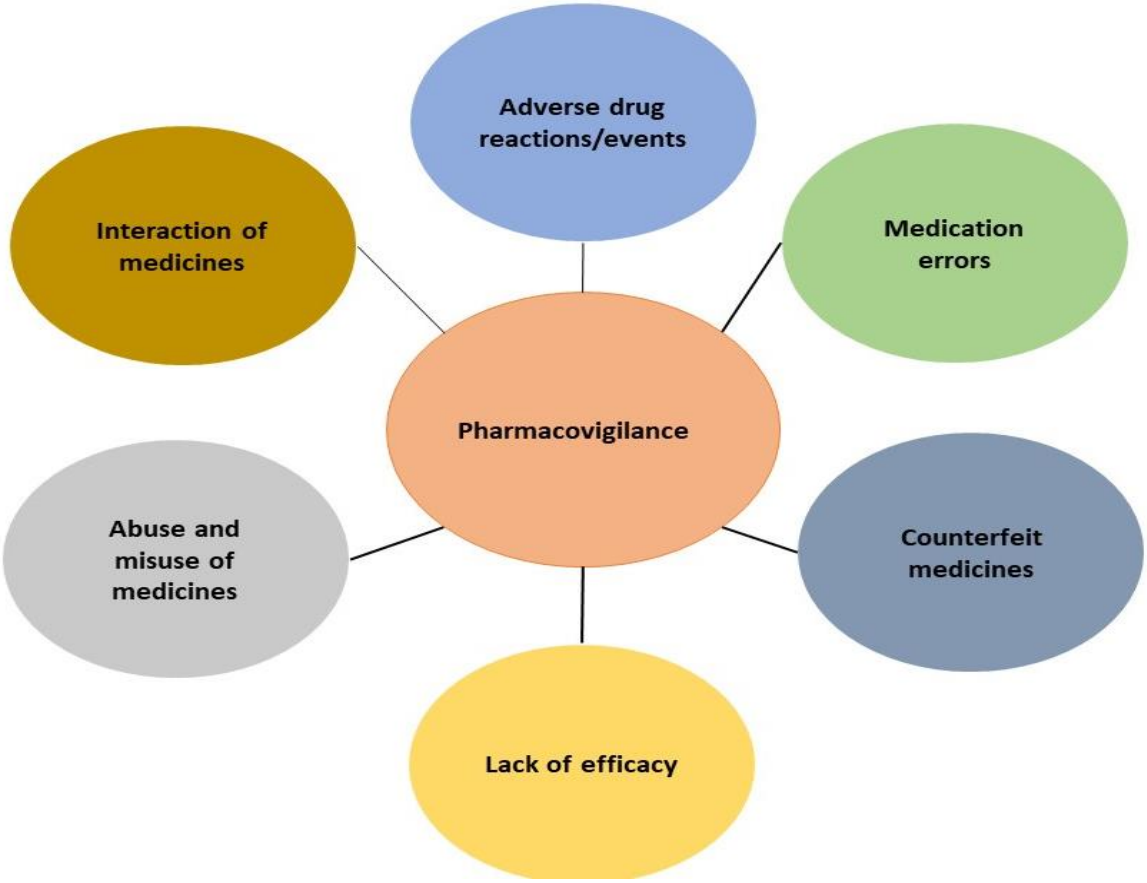

Figure 1.1: Scope of Pharmacovigilance (WHO, 2015, p.2)

1.3 Adverse Drug Reactions

1.3.1 Definition and Terminology

According to the WHO (1972), an adverse drug reaction (ADR) is defined as “any response to a drug that is noxious and unintended and occurs at doses normally used in a man for prophylaxis, diagnosis, or therapy of a disease or the modification of a physiological function”. This definition has expanded over time along with the activities related to post-marketing surveillance. In 1995, a subtle clarification regarding the definition of ADR was included in the International Conference on Harmonization. The definition of an ADR was modified to include any noxious and unintended response to a medicinal product related to “any dose” (Guideline, ICH Harmonized Tripartite, 1994).

According to the South African Medicines and Related Substances Act (101 of 1965), an ADR is defined as “a response to a medicine in humans which is noxious and unintended, including lack of efficacy, and which occurs at doses normally used in man and which can also result from an overdose, misuse or abuse of a medicine” (SAHPRA, 2020). Simply put, an ADR is considered a reaction to a drug not only when used under marketing authorization terms but also as a consequence of off-label use, medication errors, or intentional inappropriate use.

Further to the modifications in the definition of an ADR, some other terms such as “adverse event” and “side effect” have often generated confusion. Although sometimes used interchangeably with ADRs, they have slight differences worthy of note. Table 1.1 provides a summary and outlines the differences between these key terms.

Table 1.1 Summary of Definitions

Term	Definition	Example
	Harm occurred	
Adverse drug reaction (ADR)	- Any untoward medical occurrence or harm with a "possible causal relationship" with a drug at normal doses - Effective definition in clinical practice: harm caused by the appropriate or inappropriate use of a drug. Also known as adverse drug event (ADE)	Congestive heart failure from metoprolol Hematoma from tirofiban overdose
Adverse event (AE)	Untoward medical occurrence or harm in a patient being administered a drug "but not necessarily caused" by the drug	Traumatic death while taking lovastatin
	Harm may have occurred	
Side effect (SE)	- A usually predictable or dose-dependent effect of a drug that is not the principal effect for which the drug was chosen - It may be beneficial or harmful	Aspirin (a blood-thinning medicine) may cause nose bleeds or bruises
Medication error (ME)	Any preventable event that may cause or lead to the inappropriate use of a drug that may or may not result in harm	Failure to renew prednisolone order on transfer to a medical ward

Sources: Edwards and Aronson, 2000; Cobert and Biron, 2002; Gurwitz *et al.*, 2000; SAHPRA, 2020

1.3.2 Classification of Adverse Drug Reactions

Adverse drug reactions have been classified in different ways based on the onset, type, and severity of the reaction.

- **Onset of reaction**: Acute (<60 minutes); Sub-acute (1 – 24 hours); Latent (>2 days)
- **Severity**: Hartwig *et al*. (1992), defined the term "severity" as the degree of intensity of a reaction, classified as "mild", "moderate", "severe", or "lethal". An ADR is classified as "mild" when no antidote or treatment is required, and no hospitalization is needed.

"Moderate" ADRs require treatment dosage modification, but there is no need for discontinuation of therapy, and hospitalization may be prolonged by at least one day. "Severe" class includes all potentially life-threatening reactions and may require discontinuation of drug therapy and special treatment. "Lethal" ADRs directly or indirectly contribute to patients' death (Hartwig, Siegel and Schneider, 1992).

- **Serious adverse drug reaction**: Any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospital admission or prolongation of existing hospitalization, causes a birth defect or congenital anomaly, results in persistent or significant disability or incapacity, or is judged to be medically relevant by the reviewing healthcare professional (WHO, 2002b).
- **Reaction type (with mnemonics)**: According to Wills and Brown (1999), ADRs can be classified into nine different types: Type A (Augmented), Type B (Bizarre), Type C (Chemical), Type D (Delayed), Type E (Exit), Type F (Familial), Type G (Genotoxicity), Type H (Hypersensitivity), Type U (Unclassified). Table 1.2 summarizes the different types of ADRs based on this categorization.

Table 1.2: Classification of Adverse Drug Reactions (Wills and Brown, 1999)

ADR Type	Characteristics	Examples
A (Augmented)	Very common, dose-dependent, can be predicted from known pharmacology of a drug, usually alleviated by a dose reduction	Beta-blockers- bradycardia Anticoagulants- bleeding
B (Bizarre)	Not dose-dependent, cannot be predicted from the pharmacology of the drug, individual patient factors important in predisposition	Penicillin-anaphylaxis Anticoagulant- hypersensitivity
C (Chemical)	Biological characteristics based on the chemical structure of the drug or metabolite	Paracetamol- hepatotoxicity
D (Delayed)	Occur after many years of drug exposure, and it may be due to an accumulation of metabolites in the body	Chemotherapy- secondary tumours Analgesics- nephropathy
E (Exit or End of Treatment)	Withdrawal reactions, begin when the drug is stopped abruptly, or the dose is reduced	Phenytoin withdrawal- seizures Steroid withdrawal- adrenocortical insufficiency

F (Familial)	Occurs in genetically predisposed patients by lack or mutation of certain genes	Primaquine- hemolysis in patients with 6-GPD deficiency
G (Genotoxicity)	Developmental toxicity, irreversible genetic damage by teratogens	Thalidomide- teratogenicity ACE-inhibitors- hypoplasia of organs
H (Hypersensitivity)	Involves activation of the immune system, antigen-antibody reactions	Methyldopa- haemolytic anaemia Penicillin- anaphylaxis
U (Unclassified)	Reactions in which the mechanism is not understood	Simvastatin- taste disturbances

1.3.3 Global and Local Burden of Adverse Drug Reactions

Adverse drug reactions affect different categories of people regardless of age, gender, or race and have a significant economic and clinical impact (Pirmohamed *et al*., 2004). Lazarou and colleagues estimated ADRs to be among the top six main causes of death in the United States (USA), with serious ADRs accounting for 6.7% of hospitalized admissions (Lazarou, Pomeranz and Corey, 1998). Multiple studies have estimated the burden of ADRs across the globe; in Australia, ADRs constitute 5.7-18.8% of hospital admissions, 4.2-30% of admissions in the USA and Canada, 6.5% of admissions in the United Kingdom (UK), and 2.5-10.6% of admissions in Europe (Pirmohamed *et al*., 2004; Howard *et al.*, 2007).

Many developing countries are posed with an even greater burden of ADRs due to the prevalence of inappropriate medicine use, fake or adulterated drugs, and concomitant use of herbal or traditional remedies (Isah *et al.*, 2012). Additionally, the high burden of communicable diseases and the growing trend of non-communicable diseases such as cancer further raise this concern (Coovadia *et al.*, 2009; Isah *et al.*, 2012). In South Africa, although data on ADR reporting is limited, a few studies have revealed the pattern of ADRs (Mehta *et al*., 2008; Mouton *et al.*, 2015; Truter, Schellack and Meyer, 2017). In a study conducted by Mehta *et al*. (2008), approximately 6.3% of admissions were due to an ADR, and 6.3% of patients developed a significant ADR during hospitalization. A cross-sectional survey conducted in four hospitals in South Africa also revealed that ADRs contributed to the death of 2.9% of medical admissions, and about 16% of mortality was related to the ADRs (Mouton *et al.*, 2015).

In addition to the clinical burden, ADRs have a notable economic impact on patients and healthcare systems. Many countries spend between 15% to 20% of their healthcare budgets to manage drug-related problems (Pirmohamed *et al*., 2004; Rajakannan *et al*., 2013; Sultana, Cutroneo and Trifirò, 2013; Qing- ping *et al*., 2014; Roughead, Semple and Rosenfeld, 2016). For instance, in the USA, there is an estimated cost of up to $30.1 billion yearly associated with ADRs and their management (Sultana, Cutroneo and Trifirò, 2013). This cost may be due to increased or prolonged hospital admissions, additional clinical examinations in more serious cases, or the use of another medication in treating a symptom that is often an unrecognized ADR (Sultana, Cutroneo and Trifirò, 2013). The economic burden of ADRs in Europe is enormous as described by Pirmohamed *et al*. (2004); in the UK alone, ADRs were estimated at €466 million annually. Similarly, Parekh *et al*. (2018) revealed that the annual post-discharge medication-related harm in geriatric patients costs about €400 million to the National Health Service (NHS). A large fraction of this cost was attributable to hospital re-admissions (Parekh *et al*. 2018). However, this was a moderate estimate as it excluded indirect costs from wasted medicines due to non-adherence, and social costs such as the cost of absent days from work to support ill relatives. In South Africa, there is a dearth of data on the economic impact of ADRs. However, a recent study assessing the cost of managing severe cutaneous ADRs to first-line tuberculosis therapy revealed an estimate of $ 5,831 (R91,080) per patient, of which hospitalization accounted for 62% of this cost (Knight *et al*., 2019).

In general, these highlighted estimates underscore the importance of drug safety surveillance, given that 32% to 69% of drug-related hospitalizations have been reported as possibly or definitely preventable (Sharma *et al*., 2018). While drug surveillance generally aims to improve patient safety, it would also minimize costs spent on ADRs which can be diverted to more pressing healthcare needs.

1.4 Global Pharmacovigilance

Pharmacovigilance began due to some medication mishaps, particularly the famous Thalidomide disaster in the l960s. Thalidomide underwent clinical trials and was declared virtually free from side effects before its release into the market. However, these tests did not examine the effects of the drug during pregnancy (Lenz, 1988). Sadly, pregnant women who took this drug delivered babies with phocomelia, a congenital malformation in which the limbs of about ten thousand

babies were underdeveloped (Miller, 1991). This devastating incident led to the first systematic efforts to address drug safety issues globally.

In an effort to prevent such drug catastrophes, the sixteenth World Health Assembly of 1963 adopted a concept known as the WHO Programme for International Drug Monitoring (PIDM) (WHO, 2002a). In 1968, the WHO PIDM began with ten founding member countries: Canada, Czechoslovakia, Ireland, Sweden, Germany, Netherlands, New Zealand, Australia, the UK, and the USA (UMC, 2021). The goal of the PIDM was to ensure that individual countries were alerted to patterns of drug safety issues emerging across the world, which might not be evident from the local data of a specific country alone. Currently, the WHO PIDM consists of a collaboration of 149 full member countries and 23 associate members who are in the process of establishing a functional PV system (UMC, 2021). These countries work nationally and collaborate internationally to identify, review, and monitor any harm caused by medicines and establish global PV standards and systems.

In 1978, the Uppsala Monitoring Centre (UMC) in Sweden became responsible for coordinating and collating suspected ADR reports from member countries' national PV centres on behalf of the WHO (UMC, 2021). The UMC manages VigiBase, the WHO ADR database, with over 28 million case reports (UMC, 2021). VigiBase is a prime resource for generating safety signals, which are reported information on a possible causal link between a drug and an adverse reaction, where the relationship has not been sufficiently documented or is previously unknown (Edwards and Aronson, 2000; Linquidist, 2008). Signals are usually generated from more than one single report of a suspected ADR (Edwards and Aronson, 2000).

Globally, the WHO mandates member countries to submit suspected ADR reports to the VigiBase (Ampadu *et al*., 2016). For a country to be fully accepted into the WHO PIDM, a minimum of 20 ADR reports collected in the national PV programme should be submitted to the UMC (Olsson, 1998; UMC, 2021). An ADR report is considered valid with the following basic requirements: an identifiable patient, an identifiable reporter, an adverse drug reaction, and at least one suspect drug (UMC, 2012). Reports may or may not contain evidence of a causal link between the drug and the ADR (Linquidist, 2008). According to the WHO guidelines, the UMC integrates reported data

from countries that meet the "minimum requirements for a functional pharmacovigilance system" (WHO, 2010).

Table 1.3 Minimum Requirements for a Functional Pharmacovigilance System

1.	A national pharmacovigilance centre with designated staff (at least one full time), clear mandates, stable basic funding, well-defined structures and roles, and collaborating with the WHO PIDM
2.	The existence of a national spontaneous reporting system with a national individual case safety report (ICSR) form. An ICSR is a document in a specific format for the reporting of one or several suspected adverse reactions to a medicine that occur in a single patient at a specific point in time.
3.	A national database or system for collating and managing ADR reports
4.	A national ADR or pharmacovigilance advisory committee able to provide technical assistance on case investigation, risk assessment, risk management, causality assessment, and where necessary, crisis management, including crisis communication
5.	A clear communication strategy for routine communication and crises communication

Source: WHO, 2010

1.5 Types of ADR Reporting: Passive and Active

Globally, two distinct approaches to ADR reporting have been identified: passive reporting and active reporting (Weaver, Willy and Avigan, 2008).

1.5.1 Passive Reporting

Passive reporting, also known as spontaneous reporting, is the most common form of ADR reporting in the world and constitutes most of the reports in VigiBase (Hazell and Shakir, 2006). It involves the voluntary reporting of ADRs by healthcare professionals, patients, and pharmaceutical manufacturers to their respective national PV centres as they witness a reaction (Kasliwal, 2012). This method is cost-effective and allows for the continuous monitoring of all medicines used in real-life situations. For instance, spontaneous reporting led to the discovery of angioedema relating to the use of angiotensin-converting enzyme inhibitors in black patients (McDowell, Coleman and Ferner, 2006).

Spontaneous reporting has also remarkably led to the detection of new, rare, or serious ADRs throughout history (Kennedy, Goldman and Lillie, 2000; Noren and Edwards, 2009). A clear example is the case of fatal rhabdomyolysis associated with cerivastatin which led to 52 deaths

and subsequent drug withdrawal from the USA market (Staffa, Chang and Green, 2002). While this system appears to be beneficial in many ways, certain factors limit its impact. Such factors include significant under-reporting of ADRs and uncertainty of the causal relationship between drugs and the reactions (Hazell and Shakir, 2006).

1.5.2 Active Reporting

Active reporting aims to investigate the causal relationship between drugs and adverse reactions (Huang, Moon and Segal, 2014). It involves targeted reporting and cohort event monitoring (CEM). Targeted reporting is a system of intensified ADR reporting within a specific group of patients (Pal *et al*., 2013). In this system, healthcare professionals are required to complete a series of questionnaires and detail all relevant information, and data from prescriptions are analyzed (Harmark and van Grootheest, 2012). This method aims to minimize under-reporting, which is a significant drawback of the spontaneous reporting method (Harmark and van Grootheest, 2012). When used in conjunction with spontaneous reporting, targeted reporting is also a valuable tool to provide more specific information about specific ADRs (Pal *et al*., 2013). For instance, in 2015, targeted reporting was conducted in two public health facilities in Uganda to monitor suspected nephrotoxicity among patients receiving highly active antiretroviral therapy (HAART) (Ndagije *et al*., 2015).

On the other hand, cohort event monitoring programmes are designed to monitor the safety profile of certain medicines and involve the conduction of "prospective observational cohort" studies in the early post-marketing phase (Pal *et al.*, 2013). Patients are enrolled into a cohort and actively followed up during treatment to record all adverse events, not just suspected ADRs (Pal *et al.*, 2013). In South Africa, CEM is used to monitor medicines used in managing tuberculosis and HIV/AIDS (Mehta *et al.*, 2017). The goal of this programme is to consistently collect data to improve the treatment outcomes of patients on chronic medicines (Dlamini *et al*., 2014). Table 1.4 summarizes the ADR reporting types and highlights key differences.

Table 1.4 Types of ADR Reporting

	Passive	Active	
	Spontaneous Reporting	**Targeted Reporting**	**Cohort Event Monitoring**
Medicine	All medicines (monitors all through the life cycle of medicine)	Specific medicines	Specific medicines
Population	All exposed individuals	Defined population	Defined cohort
Reports	All ADRs	Specific ADRs	All events
Advantages	- Relatively inexpensive - Covers a larger population - Easy to establish - Least labour intensive	- Can utilize existing ADR reporting infrastructure - Targets specific issues of concern (ADR, medicine, patient group) - Captures useful information (less background noise)	- Characterizes known reactions - Detects signals of unrecognized reactions - Identifies interactions with other medicines - Assesses safety in pregnancy and lactation - Identifies risk factors of ADRs
Disadvantages	- Inherent under-reporting - Reporting bias - Uncertainty of causal relationship of ADR with drug - Affected by weber effect (maximum ADRs reported in first two years of launching a medicine and then keeps on decreasing)	- It minimizes but does not entirely curb under-reporting - May limit reporting only to specific ADRs - Relies on the diagnostic capability of the reporter	-Cost intensive

1.6 Global and Local Pharmacovigilance Systems

1.6.1 Stakeholders in National Pharmacovigilance

In the past, the safety of drugs was habitually the exclusive responsibility of the pharmaceutical industries manufacturing medicines and the regulatory agencies authorizing their use. Currently, more key players are required for effective pharmacovigilance. At the national level, the safety of medicines is now the responsibility of the pharmaceutical industry, drug regulators, healthcare professionals, patients, and the public (WHO, 2015, p.3). An optimal relationship and collaboration among all stakeholders are critical to the success of a national PV programme. Figure 1.2 shows the key PV stakeholders at a national level.

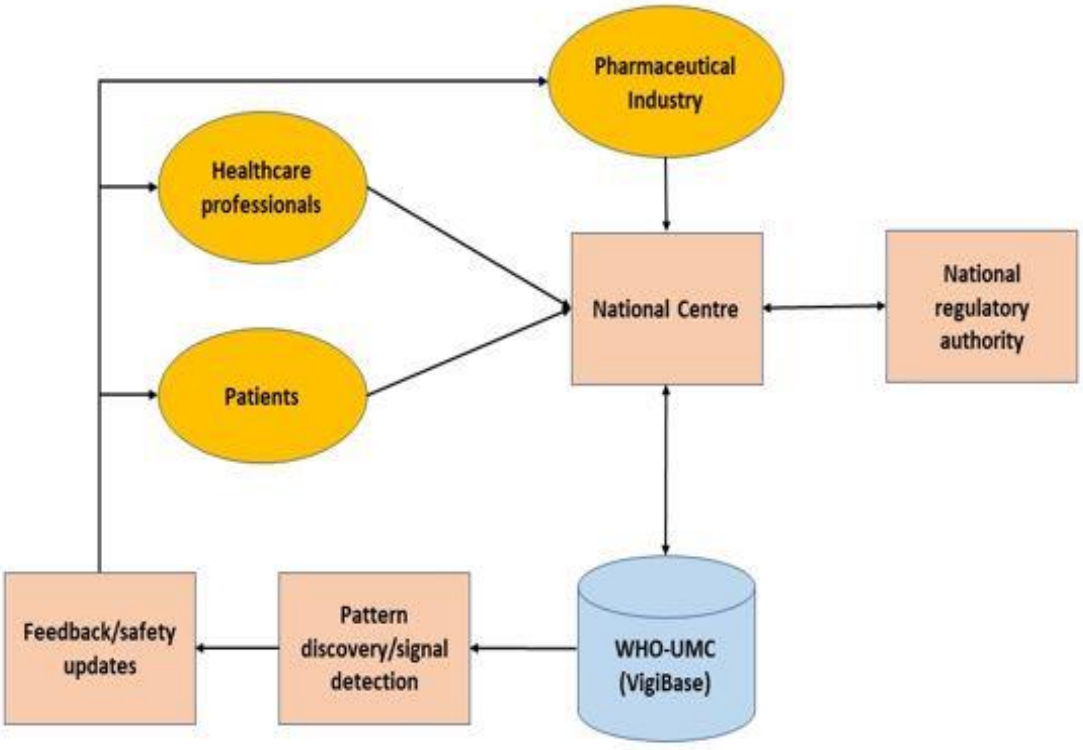

Figure 1.2: Stakeholders Involved in Pharmacovigilance

1.6.2 Overview of Pharmacovigilance Across Different Continents

The operations of national PV systems differ between WHO PIDM member countries. For instance, in some countries, ADRs are reported directly to a national centre that undertakes regulatory actions. Other countries use decentralized systems in which ADRs are first reported to regional centres before being forwarded to the national centre (WHO, 2015, p.3). Overall, the development of PV may depend on the country's healthcare system as government support is needed for national coordination (Ampadu *et al*., 2018). The PV profiles within the 5 continents of the world (Europe, Asia, Americas, Oceania, and Africa) are summarized in Table 1.5, highlighting their different regulatory bodies and ADR reporting frameworks.

Table 1.5: Pharmacovigilance Profiles Across Various Continents

Continent/ Country	Regulatory Authority	Available guidelines/ mandates/ roles	Joined the WHO PIDM	Reporting type or programme/ ADR database/ PV Advisory Committee	Additional notes
AMERICAS					
United States of America	Food and Drug Administration (FDA, 2021)	- Serious and unexpected ADEs are expedited by the manufacturer to the FDA within 15 days of receipt of the ADE (Mayer *et al.*, 2010)	1968	- Majorly spontaneous reporting using the Medwatch programme founded in 1993 (Craigle, 2007) - FDA Adverse Event Reporting System database (FAERS, 2021)	FAERS data has contributed to over 50% of all post-marketing safety-related drug label changes (Lester *et al.*, 2013)
Canada	Health Canada (Health Canada, 2019)	- Industries are mandated to submit ADR reports (Health Canada, 2018) - Hospitals are mandated to report all "serious ADRs or MDIs to Health Canada within 30 days (Health Canada, 2019)	1968	- Spontaneous reporting - Canada Vigilance Adverse Reaction Online database	

EUROPE	European Medicines Agency (EMA, 2021a)	- Marketing authorization holders are legally obligated to report ADRs (EMA, 2018) - Direct consumer reporting is predominant in most EU PV systems by Directive 2010/84/EU and Regulation No. 1235/2010) (European Parliament and Council of the EU, 2010)	Six EU countries joined in 1968	- Spontaneous reporting - Eudravigilance database was developed in 2001 - Causality assessment; likelihood that medicine caused an ADR is evaluated in some EU countries, e.g., Italy, France, and Spain, before inclusion in the national database (Olivier and Montastruc, 2006; Mazzitello *et al.*, 2013). - PRAC evaluates safety signals from EudraVigilance and recommends regulatory actions (EMA, 2021b)	- EU PV is highly advanced and robust - In 2020, 1,800,000 ICSRs were sent to WHO from EudraVigilance, making it a major contributor to the VigiBase (EMA, 2021a)
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA, 2021)	Marketing authorization holders must send all UK ICSRs and serious non-UK ICSRs to the MHRA (MHRA, 2014)	1968	Spontaneous reporting through the Yellow Card Reporting Scheme (McLernon *et al.*, 2010)	
ASIA					- In Asia, PV systems vary widely due to differences in geographical, cultural and medical practices
Korea	Ministry of Food and Drug Safety (MFDS, 2021)	- Pharmaceutical companies and pharmacies are obligated to report ADRs (Kang *et al.*, 2017)	1992	- Spontaneous reporting - Decentralized systems: regional PV centres (RPVC) facilitate ADR surveillance (Kang *et al.*, 2017) - Korea Adverse Reporting System (KAERS) database was developed in 2012	- Each RPVC monitors AE reports within the centre and external reports from local clinics and pharmacies (Kang *et al.*, 2017)

				- KIDS investigates causality in ADR reports (Shin *et al.*, 2014)	- RPVC also performs intensive monitoring on special populations (paediatrics, geriatrics)
China	National Medical Products Administration (NMPA, 2021)	-Regional centres to report all "new" and "serious" ADRs/ADEs within 3 days to the national centre (Zhao *et al*., 2018) - Other ADR/ADE reports are sent from the regional centres to the national centre quarterly (Zhao *et al*., 2018)	1998	-Spontaneous reporting by medical institutions, manufacturers and pharmacies, and drug distributors -Active surveillance (intensive safety monitoring programme) - Decentralized PV system: ADRs submitted to regional centres (Zhao *et al*., 2018)	No mandatory ADR reporting requirement for pharmaceutical manufacturers (Zhao *et al*., 2018)
OCEANIA					
Australia	Therapeutic Goods Administration (TGA, 2020)	-Pharmaceutical companies are mandated to report all serious ADRs within 72 hours (Yadav, 2008)	1968	- Spontaneous: voluntary reporting through the "blue card" system (Yadav, 2008) -Database of Adverse Event Notification (DAEN) -ADRAC monitors drug surveillance (TGA, 2020)	-Majority of ADR reports come from pharmaceutical companies (64.2%) (TGA, 2020)
AFRICA					

South Africa	South African Health Products Regulatory Authority (SAHPRA, 2021)	-Holders of the certificate of registration of medicines are mandated to submit serious and non-serious ADR reports within 15 days of a reaction (SAHPRA, 2020) -Periodic Safety Update Reports are mandatory	1992	-Spontaneous/active reporting -ADR and Quality Problem Report Form - Decentralized PV system -PV Advisory Committee (Staff = 1 pharmacist + 6 external experts) (Maigetter *et al*., 2015)	

1.6.3 Pharmacovigilance in Africa

Compared to most developed countries, Africa lagged in joining the global PV programme (Ampadu *et al*., 2016). Morocco and South Africa were the first African countries to join the WHO PIDM in 1992 (Isah *et al.*, 2012). Since then, African members have gradually increased from 2 to 41 full members, with four associate members who are in the process of instituting a functioning PV system (UMC, 2021).

Pharmacovigilance in Africa is still in its developing stages, and this is reflected in the total number of ICSRs submitted to the VigiBase. As of 2015, African members had cumulatively submitted 103,499 ICSRs to the VigiBase (0.88 % of global ICSRs), a tiny fraction of the total reports in the database (Ampadu *et al*., 2016). Multiple studies have highlighted major health system factors affecting the growth of PV in Africa (Sevene *et al*., 2008; Aagaard *et al.*, 2012; Isah *et al*., 2012). Weak national health infrastructures and systems, poor understanding and lack of PV in the formal curriculum, and low interest of healthcare professionals are some of the factors reported (Sevene *et al*., 2008; Aagaard *et al.*, 2012; Isah *et al*., 2012).

Pharmacovigilance systems operational in African countries are essentially based on spontaneous reporting, facilitated by a reporting tool, Vigiflow, which enables online transmission of ICSRs to the VigiBase (Isah *et al*., 2012). Complementary methods such as case-control studies required for signal detection and assessment are yet to be fully developed and applied in the African setting (Isah *et al.*, 2012). However, cohort event monitoring has been introduced to augment the spontaneous reporting system. The efficient deployment of these complementary methods would improve the safety of medicines and strengthen PV in Africa. Additionally, continuous training

using the WHO International Society of Pharmacovigilance (ISoP) PV curriculum would support standardized PV education and contribute to improved ADR reporting from Africa (Beckmann *et al*., 2014).

1.6.4 Pharmacovigilance in South Africa

The Medicines and Related Substances Control Act 101 was promulgated in 1965 to regulate the manufacture and supply of medicines within South Africa (Mehta *et al.*, 2017). In 1987, the Medicines Control Council (MCC) established the National Adverse Drug Event Monitoring Centre (NADEMC) to locally monitor ADR reports submitted by healthcare professionals, pharmaceutical industries, and patients. The NADEMC oversees the safety of medicines by managing, collating, and reviewing suspected ADRs to detect patterns of poorly understood or unknown ADRs (Maigetter *et al.*, 2015; Mehta *et al.*, 2017) In 1992, South Africa became the first country in Africa to join the WHO PIDM after meeting the minimum requirements for a functional PV system (Mehta, Blockman and Maartens, 2014). Subsequently, the National Department of Health (NDoH) established a national pharmacovigilance centre (NPC) in 2004, to collect and collate safety reports from public health programmes such as HIV/AIDS treatment schemes (Dheda, 2016). South Africa's PV operations are currently directed by the South African Health Products Regulatory Authority (SAHPRA) which was formerly known as the Medicines Control Council (SAHPRA, 2021). The SAHPRA is responsible for ensuring that medicines meet the required standards of safety, efficacy, and quality to ensure patient health and wellbeing (SAHPRA, 2021). Fig 1.3 shows the basic pharmacovigilance events that have occurred in South Africa.

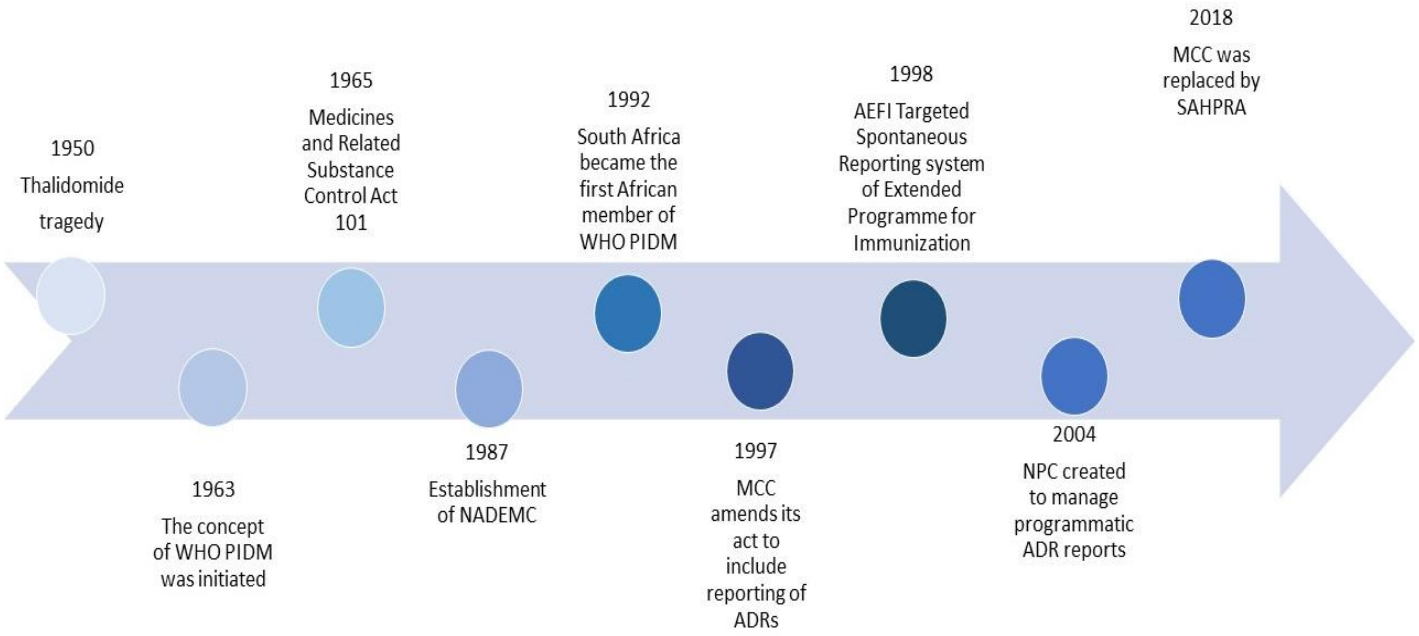

Figure 1.3: Basic Pharmacovigilance Events in the South African Context

Pharmacovigilance in South Africa is categorized into two pools: regulatory and programmatic (Figure 1.4). Regulatory PV monitors all medicines available in the country through the spontaneous reports submitted to the NADEMC. Programmatic PV is divided into passive and active surveillance (Mehta *et al.*, 2017). The active surveillance system has primarily focused on investigating the effects of HIV/AIDS and tuberculosis medicines, with resultant positive public health interventions (Mehta *et al.*, 2017). However, it is crucial to pay more attention to drugs used in treating non-communicable diseases such as cancer and cardiovascular diseases since these conditions are significant contributors to drug-related hospitalizations and healthcare costs (Tipping, Kalula and Badri, 2006). Figure 1.4 illustrates the PV bodies in South Africa, highlighting the activities and channels for locally monitoring risks associated with medicines.

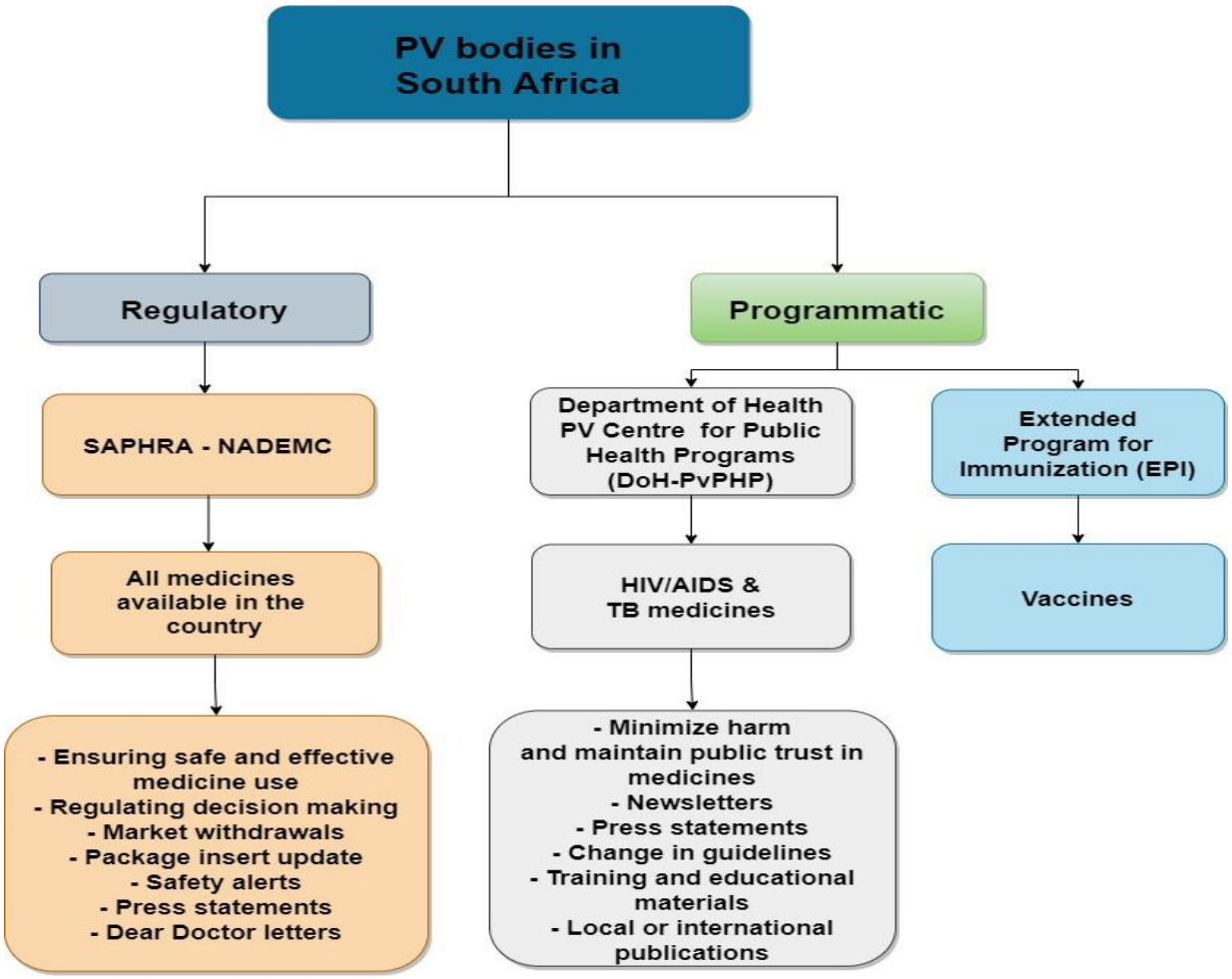

Figure 1.4: Pharmacovigilance Bodies in South Africa (Mehta, Blockman and Maartens, 2014; Maigetter *et al*., 2015; Mehta *et al*., 2017)

In the clinical setting, PV advisory committees are set up to facilitate the reporting of ADRs to the national centre, and allow for easier communication and resolution of drug issues within the hospital (WHO, 2003). In South Africa, these committees, known as Pharmacy and Therapeutics Committees (PTCs), manage drug selection, procurement, and use, and oversee the reporting of ADRs within the hospital environment (WHO, 2003). These forums provide an avenue through which public sector institutions consolidate and report ADR data to the national centre. Moreover, they provide platforms for feedback on the clinical management of ADRs. Pharmacy and Therapeutics Committees improve rational drug use when they are used effectively, and the WHO is committed to helping these committees function efficiently in developing countries (WHO, 2003). "The National Policy for the Establishment and Functioning of Pharmacy and Therapeutics Committees in South Africa" issued by the NDoH outlines the goals and policies for an effective operation of PTCs (National Department of Health South Africa, 2015). The members of a PTC

are required to have diverse expertise and skills to form an advisory committee that provides a holistic view (National Department of Health South Africa, 2015).

Unlike the public sector, the private hospital sector in South Africa has no established ADR reporting system and there is limited information regarding ADR reporting. Although healthcare professionals in this sector are encouraged and professionally required to report ADRs, the healthcare professional's knowledge and resolve determine how much is reported (Pimpalkhute *et al*., 2012).

The pharmaceutical industry has a robust reporting system comprising an assigned full-time PV officer. Also, companies are required to submit periodic safety update reports (PSURs) at specific intervals following drug approval (Maigetter *et al*., 2015). The SAHPRA, formerly known as the MCC, issued guidelines on reporting ADRs titled: "Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa". This document outlines the relevant terminology related to ADRs and the process of reporting (SAHPRA, 2020). It places no responsibility on healthcare professionals (such as pharmacists, doctors, or nurses) to report ADRs despite being the most likely first contact point. Holders of the certificate of registration of medicines are rather charged with the responsibility of reporting ADRs (SAHPRA, 2020). According to the SAHPRA guidelines, non-serious and serious ADR reports should be submitted to the national centre within 15 days of the reaction using the authorized national ICSR form (SAHPRA, 2020). The preferred form in South Africa is the "Adverse Drug Reaction and Quality Problem Report Form" (SAHPRA, 2020). Institutions are also allowed to use independent reporting forms provided that the relevant information is available. In order to ensure an effective feedback process, the reporting healthcare professional should be kept informed of progress and final outcomes (Keyter *et al.*, 2018). Unfortunately, healthcare professionals are often not given useful feedback on reported cases, which could result in a lack of motivation to report (Maigetter *et al*., 2015).

Since an official PV system began operation in 1992, South Africa has reported only 28,609 ICSRs to VigiBase, which represents 0.24% of all global reports. (Ampadu *et al.*, 2016). Within a more global context, South Africa seems to lag. Most often, data is not being incorporated into the national system, which is apparent from the little number of reports submitted (Maigetter *et al*., 2015). Reasons may be due to the complexity of the PV system resulting from many possible arms of reporting. While South Africa has a functioning PV system, reporting channels are quite ambiguous and confusing for healthcare professionals (Maigetter *et al*., 2015). Also, there is

insufficient collaboration between various health sectors, particularly the pharmaceutical industry, resulting in a limited national database (Mehta, Blockman and Maartens, 2014). Other key deficiencies in South Africa's PV system are lack of funding, limited training programmes, and insufficient capacity to analyze collected data (Maigetter *et al.*, 2015). Limited staffing was also reported as a significant challenge. The perception is that focusing on patients' clinical management is more important than the cumbersome paperwork involved in spontaneous reporting (Maigetter *et al.*, 2015). Improving PV in South Africa should address the importance of collaboration through consistent training.

1.7 Cancer

The generic term cancer refers to a large group of debilitating diseases characterised by the rapid development of abnormal cells that grow uncontrollably and spread to other organs; this process, known as metastasis, is the main cause of cancer death. Cancer incidence and mortality are increasing rapidly worldwide (Bray *et al.*, 2018). This is due to ageing population and the increasing prevalence and distribution of major risk factors associated with socioeconomic development, such as alcohol consumption, smoking, obesity, physical inactivity, and reproductive behaviours (Bray *et al.*, 2018). The World Health Organization (WHO) predicts that non-communicable diseases, primarily cancer, cardiovascular diseases, diabetes, and chronic respiratory diseases, would be the prevailing cause of death by 2030 (WHO, 2018). Among these diseases, cancer ranks the second leading cause of death globally, with an estimated 19.3 million newly diagnosed cases and about 10 million deaths in 2020 (WHO, 2020). About 70% of these deaths occur in low- and middle-income countries, where health systems are least equipped to manage the cancer burden (WHO, 2020). Without significant interventions, both cancer incidence and mortality are projected to increase by 47% by 2040 (Sung *et al*., 2021). Female breast cancer is the most diagnosed cancer worldwide, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0 %), prostate (7.3%), and stomach (5.6%) cancers (WHO, 2020). Lung cancer remains the most common cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers (WHO, 2020).

According to the WHO International Agency for Research on Cancer (2020), 108,168 new cases of cancer were diagnosed in South Africa. About 56,802 deaths were caused by cancer,

representing 25% of non-communicable disease-related mortality (International Agency for Research on Cancer, WHO, 2020). In South Africa, the cancer burden is predicted to increase in the coming decades, with new cancer cases estimated to be 138,000 and 175,000 in 2030 and 2040, respectively (International Agency for Research on Cancer, WHO, 2020). The five most common cancers in South Africa, in order of incidence, are breast, prostate, cervical, lung, and colorectal, while lung cancer is the main cause of cancer-related deaths (International Agency for Research on Cancer, WHO, 2020).

A deleterious economic impact significantly accompanies the incidence of cancer. In 2010, the total annual financial cost of cancer was estimated at 1.16 trillion US dollars globally, including healthcare expenditure and loss of productivity (Stewart and Wild, 2014). Recently, an analysis by IQVIA Institute for Human Data Science highlighted that oncology, immunology, and neurology will be the primary sources of growth through 2025, and oncology spending will exceed more than $260 billion by 2025, from $164 billion in 2020 (IQVIA, 2021). This estimate only covers therapeutic oncology, such as anticancer drugs and radiotherapeutics, and does not account for the supportive care of patients with cancer (IQVIA, 2021).

Cancer burden can be decreased through geared efforts towards risk reduction, and early diagnosis and treatment (WHO, 2008). Over the years, various modalities have been introduced to treat and manage cancer. The success of the treatment largely depends on the cancer type, location of tumour, and stage of the disease (Abbas and Rehman, 2018). Treatment options typically aim to cure the disease or prolong life while ensuring a good quality of life. Some of the traditional and widely used options are surgery, radiation, and chemotherapy, while modern modalities include hormone-based therapy and immunotherapy (Abbas and Rehman, 2018).

1.7.1 Chemotherapy

The increasing incidence and mortality associated with cancer have led to the rapid development of cancer therapies (Thakor and Gambhir, 2013). Of these, chemotherapy has been widely explored and used (Cheng *et al.*, 2020). Chemotherapy involves administering drugs to induce the death of cancer cells, control their spread, relieve tumour-related symptoms, and prolong patient survival (Abbas and Rehman, 2018). It can be administered in neoadjuvant, adjuvant, and combined settings (Amjad, Chidharla and Kasi, 2021). Neoadjuvant therapy is usually given before the primary treatment, while adjuvant therapy is the treatment added to initial therapy to

arrest or terminate the growth of occult cancer cells (Amjad, Chidharla and Kasi, 2021). Combined modalities like chemotherapy and radiation are typically used to shrink tumour cells before surgery as in the case of lung, anal, or head and neck cancers (Amjad, Chidharla and Kasi, 2021).

Over the past decades, several pharmacological options have been introduced to the market (Chabner, 2011). These treatments have profoundly improved the outcomes of patients with cancer. However, despite much progress, anticancer drugs are hindered by a high incidence of ADRs due to their narrow therapeutic window and associated toxicities (Ghandi *et al.,* 2005). In recent times, newer drug delivery options such as targeted cancer therapies are being introduced to curb toxicity issues (A Baudino, 2015). Nonetheless, PV of conventional chemotherapy drugs is crucial to minimize the incidence and severity of ADRs that accompany their use.

1.7.2 Anthracycline Chemotherapy

Since the 1960s, anthracyclines have formed the backbone of most cancer chemotherapy worldwide. These broad-spectrum antibiotics are derived from the bacterium Streptomyces peucetius and are used to treat many carcinomas, sarcomas, and leukaemias (Minotti *et al.*, 2004). Common drugs in this class include doxorubicin, daunorubicin, epirubicin, idarubicin, and valrubicin (Venkatesh and Kasi, 2021). Among the anthracyclines available for treatment, doxorubicin and epirubicin form the mainstay of many chemotherapy regimens in clinical practice (Kaklamani and Gradishar, 2003; Early Breast Cancer Trialists' Collaborative Group, 2005). They inhibit the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), thereby interfering with the replication and proliferation of cancer cells. Consequently, this also affects non-cancer cells in the body resulting in adverse effects ranging from mild to severe if not managed promptly. Common ADRs include nausea, vomiting, mucositis, alopecia, myelosuppression, and cardiotoxicity risk (Venkatesh and Kasi, 2021).

1.7.2.1 Doxorubicin

The FDA first approved doxorubicin in the United States in 1974. Since its approval, doxorubicin has gained widespread use as part of standard treatment guidelines for several solid tumours and haematological cancers. It is a key drug in treating bone and soft tissue sarcomas and cancers of the bladder, breast, thyroid, and ovary (Douedi and Carson, 2020). It is also used to treat Hodgkin's

lymphoma, acute myeloblastic leukaemia, acute lymphoblastic leukaemia, and small cell lung cancer (Douedi and Carson, 2020). In South Africa, doxorubicin is part of the national essential medicines used to treat breast cancer, lymphomas, and leukaemia (National Essential Medicines List Committee, 2020). It is routinely prescribed with cyclophosphamide (AC), or fluorouracil and cyclophosphamide (FAC) in breast cancer treatment (National Essential Medicines List Committee, 2020). Additionally, it is commonly combined with cyclophosphamide, vincristine sulfate, and prednisone to treat lymphomas and leukaemias (National Essential Medicines List Committee, 2020).

The growth of doxorubicin in the global market is driven by the increasing number of cancer cases and technologically advanced therapies available such as pegylated and liposomal forms (Global Industry Analysts, Inc., 2021). Additionally, growing survival rates associated with doxorubicin's use constitute a major growth driver (Global Industry Analysts, Inc., 2021). In 2020, Global Industry Analysts, Inc. estimated the global market size of doxorubicin at USD 992 million (Global Industry Analysts, Inc., 2021). This cost is expected to reach USD 1.3 billion by 2026 growing at a compound annual growth rate of 5.3% throughout the analysis period (Global Industry Analysts, Inc., 2021). In South Africa, the cost of doxorubicin-related therapy is high. A study assessing the costs of oncology medicines in South Africa revealed that the affordability of generic doxorubicin 50mg is a challenge for patients (Mattila, Babar and Suleman 2021). According to the analysis, the lowest-paid government employee would need 2.6 days' wages to purchase a one-month treatment of the cheapest generic doxorubicin from the private health sector (Mattila, Babar and Suleman 2021).

Due to doxorubicin's vesicant properties and harsh toxicity profile, it has been termed the "red devil". A study evaluating chemotherapy-related ADRs among hospitalized patients in North-West Ethiopia found a higher risk of toxicity in patients who received a doxorubicin regimen (Workalemahu, Abdela and Yenit, 2020). The commonly reported adverse reactions in literature are alopecia, nausea and vomiting, mucositis, and fatigue (Johnson-Arbor and Dubey, 2021). Other reactions include bone marrow suppression, urine discolouration after 1-2 days, hepatotoxicity, and a risk of secondary malignancy within 1-3 years after therapy (Johnson-Arbor and Dubey, 2021). Extravasation usually occurs with intravenous administration and can lead to severe tissue ulceration and necrosis which worsens over time (Johnson-Arbor and Dubey, 2021). Doxorubicin

is also notorious for its rare but serious adverse effects on the heart, limiting its long-term use. These effects include cardiac arrhythmias, myocardial infarction, and cardiomyopathy, which is characterized by symptoms of heart failure or a decrease in the ejection fraction of the left ventricle (McGowan *et al*., 2017). In a retrospective study, doxorubicin-related cardiotoxicity was reported to have an incidence of 26% and 1-year mortality of up to 50% (Swain, Whaley and Ewer, 2003). Despite the efficacy of doxorubicin in many cancer diagnoses, its administration requires careful monitoring of liver function, blood counts, and cardiac function in the clinical setting to ensure patient safety.

1.7.2.2 Epirubicin

In 1999, epirubicin was approved for use by the FDA and has been one of the most effective agents in treating patients with breast cancer both globally and locally (Kaklamani and Gradishar, 2003). It is also used for treating gastric cancer, ovarian cancer, lung cancer, Hodgkin's lymphoma, and non-Hodgkin's lymphoma (Plosker and Faulds, 1993). In South Africa, epirubicin is routinely prescribed as an integral component of adjuvant therapy for surgically removed early breast cancer (National Essential Medicines List Committee, 2020). It is typically administered over slow intravenous injection or through the intravesical route.

Epirubicin is structurally related to doxorubicin. However, epirubicin is generally safer at cumulative doses compared to doxorubicin (Khasraw, Bell and Dang, 2012). This is due to the different spatial orientation of the hydroxyl group in position 4 of the amino sugar, which is responsible for the faster elimination and reduced toxicity of epirubicin (Kaklamani and Gradishar, 2003). The most common ADRs are myelosuppression, infections, nausea, vomiting, mucositis, urine discolouration, malaise, and alopecia (Kaklamani and Gradishar, 2003). Tissue necrosis, acute myeloid leukaemia, radiation recall and local reactions, and anaphylactic reactions are less common adverse reactions (Praga *et al*., 2005; Plosker and Faulds, 1993). Epirubicin also causes transient cardiac arrhythmias and electrocardiogram changes, which may be early (acute) or late (delayed) (Fumoleau *et al.*, 2006). However, the literature suggests that epirubicin causes less cardiotoxicity than doxorubicin at cumulative doses (Khasraw, Bell and Dang, 2012). Initiation and maintenance of treatment require careful monitoring of baseline parameters and cardiac function.

Post-marketing surveillance has identified a few adverse reactions related to epirubicin administration. In 2018, the Ministry of Food and Drug Safety (MFDS), the regulatory body in the Republic of Korea, found a causal association between epirubicin and pneumonia. During the evaluation process of serious adverse event reports, the Korean Institute of Drug Safety (KIDS) reviewed a fatal serious adverse event report of *pneumocystis jirovecii* pneumonia (PCP) in a patient receiving epirubicin-containing chemotherapy (WHO, 2019). This led to the update of the drug label for epirubicin (Pharmorubicin) to include pneumonia as an ADR.

1.7.3 Methotrexate

Methotrexate is an antimetabolite chemotherapeutic agent whose use dates back to the 1940s. It was first developed as a less toxic derivative of aminopterin and then as a folic acid antagonist used to treat acute leukaemia in children (Purcell and Ettinger, 2003). Currently, methotrexate is an integral part of most cancer chemotherapies and is widely prescribed alone or in combination with other drugs. It is used to treat various cancers such as breast cancer, brain tumours, lung cancer, head, neck, and oesophageal cancers, stomach cancer, osteosarcoma, and lymphoma (Crews *et al*., 2004; Kozminski *et al*., 2020). Methotrexate can be administered orally or as an injection. A range of doses has been used to treat solid tumours; very high doses are administered through an intravenous infusion (Hannoodee and Mittal, 2021).

Methotrexate is favoured in the South African market due to its efficacy, low cost, rapid onset of action, and ease of administration (Visser and Van der Heijde, 2009). However, its use is hindered by its toxic effects. Methotrexate competitively inhibits folic acid reductase, reducing the production of tetrahydrofolic acid and blocking DNA synthesis. This process has damaging effects on cells that have a high rate of cell turnovers such as the bone marrow, gastrointestinal mucosa, and hair follicle (Al-Niaimi and Cox, 2009). Adverse drug reactions following methotrexate administration range from mild gastrointestinal effects such as mucositis and vomiting to severe reactions like myelosuppression, anaphylactic shock, acute renal failure, pulmonary symptoms, and hepatotoxicity (Al-Niaimi and Cox, 2009). Bone marrow toxicity as myelosuppression can occur due to folate deficiency and can be prevented by supplementation with folic acid (Hannoodee and Mittal, 2021). In patients with an existing hematopoietic disorder, the administration of methotrexate should be done with caution. Furthermore, methotrexate often leads to hepatotoxicity, which manifests as an increase in aminotransferases after long-term

use (Hannoodee and Mittal, 2021). With a long treatment duration, regular liver biopsies and ultrasound examinations are necessary to determine the condition of the liver (Hannoodee and Mittal, 2021).

Post-marketing surveillance has revealed some significant safety signals associated with methotrexate use. In Europe, the pharmacovigilance risk assessment committee (PRAC) published a list of safety signals in the annual report of the Eudravigilance database in 2020. Progressive multifocal leukoencephalopathy was identified, and it is part of the ADRs currently undergoing evaluation (EMA 2021c). Although a definite causality has not yet been established, the PRAC recommended the inclusion of a special warning for progressive multifocal leukoencephalopathy in the approved drug package leaflets in Europe (EMA, 2021c). This is to raise awareness of healthcare professionals and to advise patients appropriately. Additionally, literature has reported a link between medication errors and methotrexate (Moore, Walsh and Cohen, 2004; Cairns *et al.*, 2016). These errors which could arise during prescribing or dispensing methotrexate could lead to serious health consequences, including death. In 2019, the Health Product Regulatory Authority of Ireland also announced an update in the package labels for five methotrexate-containing products (Jylamvo®, Methofill®, Methotrexate®, Metoject®, and Nordimet®) to include medication errors (HPRA, 2019). This action aimed to strengthen warnings regarding dosing errors and ensure that the medicine is only prescribed and dispensed by healthcare professionals with the required expertise (HPRA, 2019).

1.8 The Role of Pharmacovigilance in Oncology

Patients on chemotherapy show a greater potential for ADRs, as highlighted by Ghandi *et al.* (2005). Adverse drug reactions following cancer therapy are one of the most important issues that patients with cancer face (Baldo *et al*., 2018). This is because chemotherapy involves the administration of immensely complex regimens with high toxicities. A study conducted in Southern India indicated that anticancer drugs are the most common drugs causing ADRs (Jose and Rao, 2006). Another study conducted by Pearce and colleagues (2017) revealed that approximately 86% of patients with cancer report at least one ADR during chemotherapy. A review of oncology medical records also found that patients experienced at least one ADR during hospitalization, and more than 40% had three or more ADRs (Lau, Stewart and Dooley, 2004).

Globally, chemotherapy-related ADRs are worrisome, contributing to increased morbidity and reduced quality of life (Ma, Wang and Chung, 2007; Niraula *et al.*, 2012; Mrugank and Hareesha, 2013). San Turgay *et al.* (2008) assessed the effect of the first chemotherapy course on the quality of life of cancer patients in Turkey. Patients undergoing chemotherapy reported feeling low energy, limited mobility due to worsened physical symptoms, low sexual desire, limited social interactions, and reduced ability to work (San Turgay, Khorshid and Eser, 2008). Simply put, the administration of chemotherapy regimens increases the potential for toxic reactions, which gradually lessens patients' quality of life.

In order to achieve optimal treatment outcomes in patients with cancer, continuous long-term treatment is essential. Unfortunately, the high incidence of ADRs and the associated impairment on quality of life often leads to patients not adhering to therapy or discontinuing it early. Lack of adherence or early discontinuation of cancer therapy has been shown to be significant predictors of disease progression, morbidity, and mortality in patients with cancer (McCowan *et al.*, 2008). A further consequence of non-adherence to treatment could be the loss of money caused by wasting already purchased drugs. If detected early, ADRs can be prevented or at least proactively managed, leading to improved adherence to therapy and better quality of life.

The need for PV is particularly relevant and urgent for medicines used to treat cancer due to inherent toxicity, even at therapeutic dosages. Moreover, cancer patients often have co-morbidities requiring multiple drugs, making their treatment complex and compromising the safety profile of their anti-cancer drugs. (Crestan *et al.*, 2020). Adverse drug reactions are so common in oncology that they often come around to being accepted as an “inevitable” consequence of these treatments (Lau, Stewart and Dooley, 2004). Additionally, ADRs are often confused for underlying patients’ clinical conditions or symptoms by physicians and are frequently underestimated and under-reported (Baldo *et al.*, 2018). The complexity of oncology makes the recognition of ADRs and their distinction from other conditions somewhat difficult and highlights the need for efficient PV (Baldo *et al.*, 2018).

1.9 Under-reporting of ADRs

Continuous reporting by health professionals and patients provides important information for PV systems at global and local levels. However, as with general medicine, ADR reporting in oncology

is limited and largely characterized by under-reporting (Baldo *et al.*, 2015). Under-reporting of ADRs is a major factor hindering the role of PV; globally, less than 10% of ADRs are reported (Hazell and Shakir, 2006). This phenomenon is even more pronounced in developing countries (Ampadu *et al.*, 2016; Aagaard *et al.*, 2012). In 2016, Ampadu and colleagues revealed the extent of under-reporting in Africa, showing that less than 1% of ADR reports in VigiBase had been submitted by 35 African countries (Ampadu *et al.*, 2016). Under-reporting results in incomplete safety data and ADRs that go undiscovered.

The reasons for under-reporting of ADRs among healthcare professionals have been widely studied (Hazel and Shakir, 2006; Isah *et al*., 2012; Gahr *et al*., 2016). Isah *et al*. (2012) highlighted common causes for under-reporting in Africa; "inability to recognize ADRs, ignorance of the reporting requirements, feeling of guilt following the occurrence of adverse effects and fear of litigation, lack of feedback from hospital administrators" were the reasons cited. In a study investigating the under-reporting of ADRs among physicians in Germany, a significant fraction of physicians reported that they only report unknown ADRs (40.9%) or severe ADRs (26.1%) (Gahr *et al.*, 2016). Frequent subjective reasons for not reporting ADRs were lack of time, the perception that the ADR reporting process is complex or requires too much time, or that reporting an ADR is unnecessary (Gahr *et al*., 2016). Baldo *et al.* (2015) highlighted under-reporting of oncology drugs as a common trend. In this study the authors noted that physicians often trivialize the reactions caused by anti-cancer drugs, considering them as "normal" and focusing instead on the efficacy of the drugs (Baldo *et al.*, 2015). Healthcare professionals sometimes do not report oncology ADRs because they think that filling PV reports or pharmaceutical industry complaints could have negative consequences on patients' therapy (Baldo *et al*., 2015). Furthermore, due to overwhelming clinical activities, oncologists often delegate the reporting function to nurses, resulting in some ADRs not being recorded (Ruiz *et al*., 2014).

A reporting standard, however, can be met if healthcare professionals have the right knowledge, attitude, and perception about ADR reporting (Pimpalkhute *et al*., 2012). According to a study by Lopez-Gonzalez and colleagues, personal and professional factors have little influence on reporting while healthcare professionals' knowledge and attitudes appear to be strongly related to reporting (Lopez-Gouzalez, Hedeiro and Figueiras, 2009). Several studies have shown differences in healthcare professionals' knowledge and attitudes towards ADR reporting across the world

(Herdeiro *et al*., 2006; Gavaza *et al.*, 2011; Schellack, Padayachee and Bogolubova, 2018; Haines *et al.*, 2020). However, the literature shows that physicians in developed countries (such as the USA) tend to have better PV knowledge and reporting practices than their counterparts in developing countries such as India, Nigeria, and Ghana (Nadew, Beyene and Beza, 2020). In an analysis conducted in South Africa's public sector hospitals, healthcare professionals' knowledge about ADR reporting was poor, while attitudes were quite positive (Schellack, Padayachee and Bogolubova, 2018). Lack of knowledge on how to report correctly, not knowing where to report, inadequate training on how to identify an ADR, and a lack of access to ADR forms were the main factors limiting reporting (Schellack, Padayachee and Bogolubova, 2018). To improve PV, healthcare professionals need to be able to recognise adverse reactions to the medicines they prescribe and dispense and should understand the ADR reporting framework.

1.10 Rationale of the Study

In oncology, the implementation of an adequate PV is particularly crucial because of the peculiarity of the toxic nature of the drugs and the complexity of the treatment regimens as highlighted by Baldo *et al*. (2018). Although chemotherapy has profoundly improved the outcomes of patients with cancer, the increasing administration of these drugs increases the risk of ADRs. Hence, continuous drug monitoring and the analysis of reported ADRs could contribute to enhancing the safety knowledge of these medicines and is essential to improving cancer patient safety.

To date, this study is the first of its kind to assess ADR patterns for specific chemotherapy drugs as reported to a global safety database. Previous PV studies have so far focused on adverse reactions generally associated with chemotherapy, reported within a particular country or geographical region (Mallik *et al*., 2007; Poddar *et al*., 2009; Prasad *et al*., 2013; Sharma *et al*., 2018). Moreover, there are very few studies examining the adverse drug reactions for specific anticancer drugs in the literature. This study focused on 3 oncology medicines, doxorubicin, epirubicin, and methotrexate because of their broad-spectrum cancer activity and their widespread use; they are routinely prescribed as single agents or in combination to treat "many types" of cancers both globally and in South Africa (National Essential Medicines List Committee, 2020;

WHO Model List of Essential Medicines, 2021). This highlights the importance of analyzing their adverse reactions to identify patterns of drug safety issues emerging across the world.

1.11 Research Question

What are the patterns of ADRs associated with the use of doxorubicin, epirubicin, and methotrexate reported to the VigiBase?

1.12 Purpose of the Study

1.12.1 Study Aim

The study aimed to analyze the global patterns of ADRs associated with the use of doxorubicin, epirubicin, and methotrexate using VigiBase data**.**

1.12.2 Study Objectives

The specific objectives of this study were:

I. To identify and quantify the top 10 ADR system organ categories for each drug according to continents.
II. To examine associations between demographic factors and the top 10 ADRs (MedDRA Preferred Terms) reported for each drug.
III. To describe serious ADRs and identify the top 30 serious ADRs reported for doxorubicin and epirubicin in VigiBase.
IV. To compare the top 50 ADRs (MedDRA Preferred Terms) identified in VigiBase for each drug with the ADRs documented on the drug package inserts in South Africa.

1.13 Significance of the Study

This study would provide relevant insights into the trends of reported adverse reactions and this could have notable implications in clinical practice globally and in South Africa. This study can lead to the generation of rare or serious adverse reactions previously unknown in literature. Likewise, new information on potential risks associated with already known ADRs could be

discovered as this study also attempts to establish associations between ADRs and patient demographic characteristics. Additionally, this study would highlight reported ADRs globally that are not included in package inserts in South Africa to alert healthcare professionals to monitor these reactions locally and this can potentially contribute to South Africa's safety data for these medicines.

In summary, this study would:

I. Provide healthcare professionals globally and in South Africa with the knowledge needed to aid early ADR identification and reporting.
II. Guide prescribers in making informed clinical decisions in cancer chemotherapy, to minimize potential risks and improve patients' quality of life.
III. Equip health policymakers with relevant information needed to improve cancer patient safety through education, advocacy, and policy formulation.
IV. Expand scientific knowledge and provide a platform upon which further pharmacovigilance studies can be built.

1.14 Chapter Summary

This chapter has provided a background into the study problem and a review of the topics relating to the research. The literature illustrates that ADRs are an imminent and immediate public health threat. In oncology, patients are even more prone to ADRs due to the highly toxic nature of the treatment regimens. However, by utilizing effective PV systems, it will be possible to minimize the risks experienced by these patients by ensuring that the medicines they use have an established safety profile. This chapter has also highlighted the systems for monitoring ADRs globally, and more elaborately in South Africa. Furthermore, it highlights the profile of the three focus drugs, the peculiarity of PV in oncology, and justifies the need for PV in oncology. Further, it gives an overview of under-reporting of ADRs as a major limitation to PV and discusses healthcare professionals' knowledge and attitudes, and factors hindering ADR reporting. Lastly, the rationale of the study is explained followed by the objectives and significance of the study. The following chapter will discuss the methods used to conduct the research.

CHAPTER 2

METHODOLOGY

2.1 Introduction

This chapter covers the methodological approach used in investigating the research problem. It includes the general design of the study, data source, ethical considerations, and the data collection process. The inclusion and exclusion criteria and data analysis process are also described. Lastly, this chapter explains how bias was minimized in this study and the limitations of the study.

2.2 Study Design

This study was a longitudinal quantitative secondary analytical study. In the medical field, a secondary analytical method involves the use of existing data collected by a different researcher for the purposes of a prior study, to pursue a research interest that is distinct from that of the original work (Boslaugh, 2007). This study involved collating, analyzing, and interpreting adverse drug reaction reports for doxorubicin, epirubicin, and methotrexate submitted to the VigiBase database.

2.3 Data Source

The data used in this study was obtained from VigiBase, the WHO global database of ICSRs (Lindquist, 2008). Each country's national pharmacovigilance centre receives reports of suspected adverse reactions from healthcare professionals, pharmaceutical industries, and patients. These reports are reviewed locally and then forwarded to the VigiBase database. VigiBase is the largest ADR repository in the world, with over 20 million suspected ADR reports submitted since 1968 by 149 member countries of the WHO PIDM (UMC, 2021). This makes VigiBase a uniquely diverse and comprehensive data source for this study.

2.4 Ethical Considerations

Permission to use data was obtained from the Uppsala Monitoring Centre (UMC) through the pharmacovigilance scientist who controls access to the VigiBase database. Data was anonymously

extracted from the database; hence no identifiable patient information was available for analysis. Ethics clearance was gotten from the University of the Witwatersrand Human Research Ethics Committee to conduct this study (Ethics No: M210866) (See Appendix C)

2.5 Data Collection/Extraction

The VigiBase data gotten from the Uppsala Monitoring Centre (UMC) contained ADR reports for doxorubicin, epirubicin, and methotrexate**.** All ADRs for doxorubicin and epirubicin reported in VigiBase from 1968 up until 30th August 2020 and for methotrexate between 1st January 2017 and 30th August 2020 were electronically captured into Microsoft Excel spreadsheets. Records retrieved for doxorubicin, epirubicin, and methotrexate had 79,319, 20,007, and 84,992 ICSRs respectively, making a total of 184,318 unique case reports and 2,766,573 ADRs (doxorubicin=1,285,300; epirubicin=202,883; methotrexate= 1,278,390). Each ICSR recorded in VigiBase is an anonymized report for an individual who experienced one or several ADRs that may be related to the use of one or more drugs. Hence, the number of ADRs reported was greater than the number of ICSRs since more than one ADR can be reported for an individual patient.

The VigiBase data captured into Microsoft Excel spreadsheets was represented according to the information recorded on each ICSR when an ADR was reported. Each ICSR was designed to capture the following information:

- **Administrative information**: This included the date the report was first accessible in VigiBase, the last date the report was updated, the type of report (such as spontaneous or targeted reporting), and the qualification of the reporter or notifier(s). Each ICSR can have more than one reporter since more than one ADR can be reported for an individual patient.
- **Patient demographic data**: Each patient's information was coded with a unique identification number, and no identifiable patient information was captured. Demographic data included: gender, the reporting continents according to the United Nations or reporting region according to the WHO, and age group. The demographic data in VigiBase were categorized according to the United Nations list of continents and not according to the reporting country. For instance, ADR reports submitted by South Africa's national pharmacovigilance centre were grouped under Africa in VigiBase. Also, patient age was categorized into predetermined age groups, and no individual patient age was recorded in the VigiBase data.

- **Information on the reported drug**: This included the name of the drug, dosage regimen, indication for drug use, route of administration, drug treatment duration, drug status as suspect/interacting or concomitant, dechallenge and rechallenge information, and information on other concomitant drugs (oncology and non-oncology drugs) reported to be used other than the suspect drug.

- **Characteristics of the reported ADR**: This included information on the MedDRA System Organ Class (SOC); providing a broad definition of the system of the body affected or the manifestation site, MedDRA Preferred Term (PT); providing a distinct medical concept describing the ADR, and MedDRA Lowest Level Term (LLT); which is how the ADR is communicated or reported in practice. Other characteristics of the reported ADR include the time to onset of the reaction, the outcome of the reaction, if the ADR was reported as serious or not, and the seriousness criteria of the ADR as defined by the WHO. According to the WHO (2002b), an ADR is categorized as "serious" if it resulted in death, is life-threatening, triggers hospitalization or prolongation of existing hospitalization, causes a birth defect or congenital anomaly, leads to persistent incapacity or disability, or is judged medically significant by the physician who reports the case.

The above information on each ICSR was extracted on Microsoft Excel spreadsheets with 33 column headings (See Appendix B). These characteristics served as variables used for analysis and examining patterns in this study.

2.6 Terminology

All reported ADRs in VigiBase have been automatically coded, either according to the WHO Adverse Reaction Terminology (WHO- ART) or the Medical Dictionary for Regulatory Activities (MedDRA) terminology (Linquidist, 2008). The MedDRA is a medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Since MedDRA is now used to retrieve data from VigiBase, ADRs originally coded in WHO-ART have automatically been mapped to corresponding MedDRA terms (Linquidist, 2008). Additionally, all reported drugs in VigiBase are allocated codes according to the WHODrug terminology, and diseases are classified based on the International Classification of Diseases (ICD) (Linquidist, 2008). These terminologies allow for structured and easy data entry and retrieval which are essential for effective and accurate analysis.

2.7 Inclusion and Exclusion Criteria

2.7.1 Inclusion criteria

All individual case safety reports in Vigibase where doxorubicin, epirubicin, and methotrexate were recorded as "suspect" or "interacting" drugs were included in this study.

2.7.2 Exclusion criteria

Exclusion criteria were as follows:

- **Combination medicines**

  All reports for drugs containing any of the suspect drugs combined with another drug(s) were excluded. For instance, a case report with a drug combination of doxorubicin and cyclophosphamide was filtered out and not included in the study. The reason for this was to rule out the possibility of a reaction due to a drug-drug interaction or an adverse reaction caused by the non-suspect medicine.

- **Concomitant drugs**

  Case reports where any of the 3 drugs (doxorubicin, epirubicin, or methotrexate) was reported as a “concomitant” drug were excluded. Since in such cases, these drugs were taken by the patients in addition to a "suspect drug" or the drug under investigation, they were considered irrelevant in this study.

- **Duplicate ADRs**

  Suspected duplicate ADRs are likely to occur in Vigibase when reports of the same ADR for an individual patient are sent from multiple sources. This could be as a result of a patient and a healthcare professional reporting the same reaction or different healthcare professionals treating the same patient reporting the same event or reaction. These duplicates are usually excluded in the VigiBase database using an automated screening method previously described in detail (Noren *et al.*, 2007). However, the final dataset retrieved for this study still contained additional duplicates of ADR reports. These duplicates were manually removed by sorting the data based on similarity in the unique case identification number, reported ADR, and suspect/interacting drug using Microsoft Excel.

2.8 Data Analysis Process

The data downloaded into Microsoft Excel spreadsheets (Version 2016) was first cleaned, sorted, and filtered based on the inclusion and exclusion criteria. After cleaning and sorting, descriptive statistics was used to summarize the categorical variables (age group, gender, continent, ADRs) using Microsoft Excel. The top 10 ADR system organ categories were summarized according to continents using frequencies and percentages. The top 50 ADRs based on MedDRA Preferred Terms were also quantified using frequency tables and kept for further analysis.

The second step of the data analysis was carried out using Stata software version 16 (StataCorp, 2019). The categorical variables (age group, gender, continent, top 10 ADRs based on MeDRA Preferred Terms) were coded with numbers for ease of analysis and imported into Stata software. The Data Editor browse tool in Stata was used to check the accuracy of the imported data and any error was corrected using this function. All the commands for data analysis were typed into the command window and the results were displayed in the results window in Stata. Pearson chi-squared test for categorical variables was done to establish significant associations between the dependent variables (the top 10 ADRs based on MedDRA Preferred Terms) and independent variables (demographic factors i.e. age group, gender, and continent) using the Stata. A p-value of less than 0.05 was considered statistically significant. Logistic regression analysis was conducted to estimate the association between the top 10 ADR (MedDRA Preferred Terms) and demographic factors. Each of the top 10 ADRs (levels) was considered as an independent outcome, that is, each reaction was taken as a binary outcome, and binary logistic regression was used to assess demographic risk factors. The results were shown as odds ratios with 95% confidence interval (CI), and a p-value < 0.05 was considered statistically significant.

The approved drug package inserts (PI) for doxorubicin, epirubicin, and methotrexate in South Africa were searched for on the SAHPRA website. A total of 6 PIs were available on the website: doxorubicin (Caelyx®, Rubexet, Cipla Doxorubicin), epirubicin (Aspen Epirubicin, Farmorubicin), methotrexate (Abitrexate®) (PI links in the bibliography). The package inserts were assessed and compared with the top 50 ADRs (MedDRA Preferred Terms) identified in VigiBase to check for patterns of new or unrecognized ADRs.

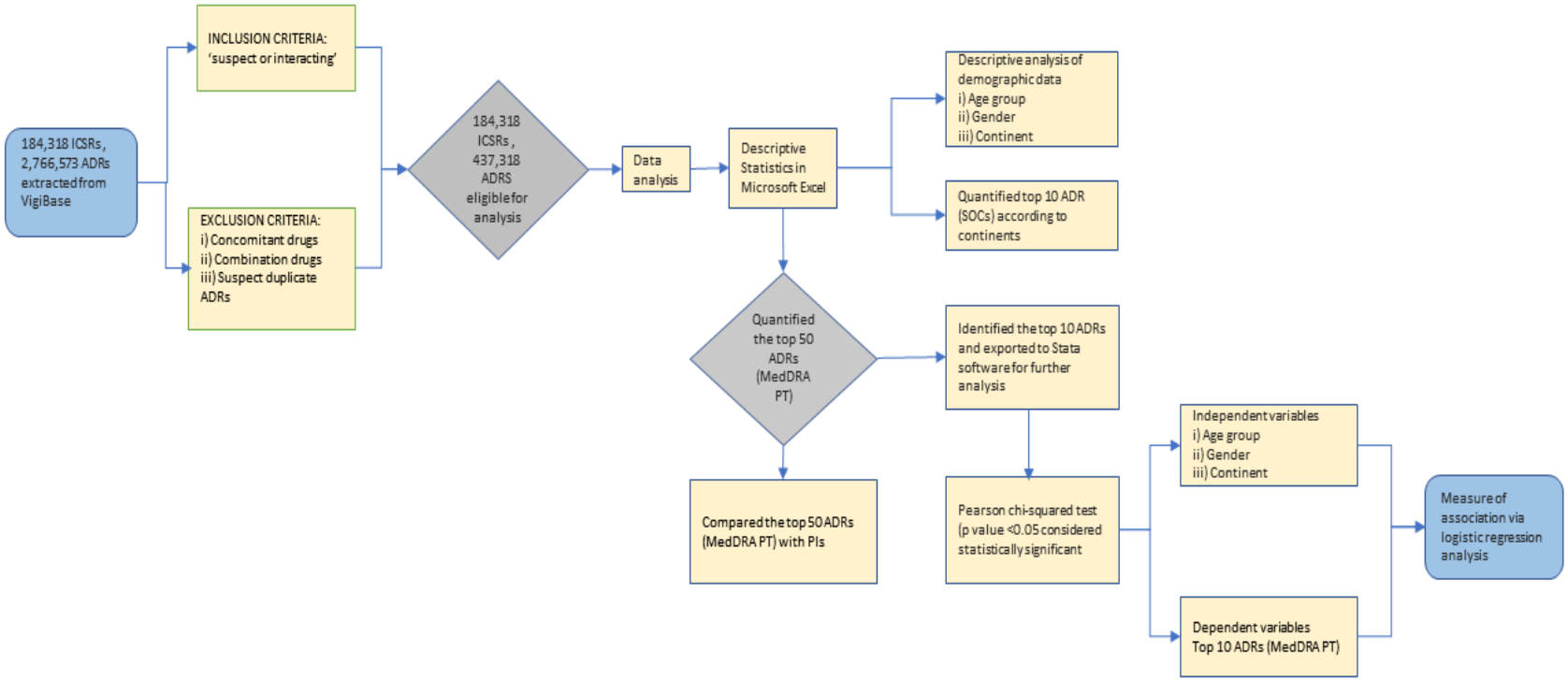

Figure 2.1: Data Analysis Flow Chart

2.9 Reliability and Validity of the Study

Validity is defined as the degree to which a certain measurement is accurate (Price, Jhangiani and Chiang, 2015; Glen, 2021). Reliability means the consistency with which a measuring instrument yields a particular result (Price, Jhangiani and Chiang, 2015; Glen, 2021). Reliability also refers to the degree to which two or more researchers obtain the same results. It can be altered if the instrument or collection procedure is changed. To ensure reliability and validity, the researcher ensured the same data extraction procedure was applied for all unique case safety reports for the 3 drugs, and uniformity of the data source was maintained. Furthermore, the data source (VigiBase database) has been previously used for similar studies and it is a valid ADR repository that suited the stated aim and objectives of this study.

2.10 Bias

Bias can be defined as any variation from the truth during research design, data collection, and analysis; it can be intentional or unintentional (Simundic, 2013). It can occur when there is no randomization of participant selection that may cause sample selection not to represent the intended population. Selection bias was limited since the study followed a secondary analytical design and there was no favour over a certain group over the other. The same inclusion and exclusion criteria were applied when reviewing the data in this study. All ICSRs for each drug were treated uniquely and variables were standardized across all drugs. Filtering and sorting techniques were also consistent across all drugs, and the same coding technique was used for all the case reports. Furthermore, a researcher bias may occur when the researcher has a personal inclination or bias towards a method or technique. In such cases, the researcher may create a predetermined hypothesis regarding the results that were obtained with the different methods. Researcher bias was minimized in this study by ensuring that consistency in the analysis was maintained throughout without exploiting analytical flexibility. Lastly, a reporting bias may happen if analysis steps are not documented in a uniform manner or if there is selective reporting of statistically significant or “clean” results. To minimize this, steps in the analysis were documented uniformly, and all analysis procedures and results were checked by supervisors regularly to prevent selective reporting of results.

2.11 Study Limitations

An important limitation of this study was under-reporting. Under-reporting of ADRs impacted the knowledge gathered in this study and does not give an accurate picture of all the actual ADRs experienced by patients in clinical practice. Also, there were missing details regarding age group, gender, and the reporting continent in the case reports. These factors may have affected the statistical power to detect variables as significant predictors during the regression analysis. Additionally, there was limited clinical information in the case reports. For instance, patients' medical history and co-morbidities were not provided. This limited a comprehensive interpretation of the patterns in this study.

CHAPTER 3

RESULTS

3.1 Introduction

This chapter presents the results from this study first in a descriptive fashion, and later using descriptive statistics. Results are mostly presented as frequencies and percentages and in tabular form. Pearson chi-squared tests shows association between variables ($p < 0.05$ significance level) while binary logistic regression reveals the magnitude of association. A total of 184,318 ICSRs (Dox=79,319; Epi=20,007; Met=84,992) and 2,766,573 ADRs (Dox=1,285,300; Epi=202,883; Met=1,278,390) were retrieved from VigiBase. After exclusion, 184,318 ICSRs (Dox=79,319; Epi=20,007; Met=84,992) and 437,318 ADRs (Dox=188,277; Epi= 38,907; Met=210,134) were eligible for analysis.

3.2 Demographic Data

Analysis showed that the majority of reports were from females (Dox= 64.65%; Epi= 84.21%; Met= 66.76%). The predominant age group was 45-65years (Dox= 38.12%; Epi= 52.10%; Met= 29.55%) excluding the unknown category. Regarding continental data, while Asia reported the highest for doxorubicin and epirubicin (Dox= 43.49%; Epi= 48.70%), Americas recorded the highest reports for methotrexate (Met= 60.53%). Africa reported the least for doxorubicin and epirubicin (Dox=0.93%; Epi= 0.55%), whereas Oceania showed the least reports for methotrexate (Met=0.51%). Physicians were the highest group of reporters (Dox=43.90%; Epi= 37.78%; Met= 45.03%). Table 3.1 summarizes the demographic characteristics of ICSRs for doxorubicin, epirubicin, and methotrexate in VigiBase.

Table 3.1: Demographic Characteristics of Individual Case Safety Reports for Doxorubicin, Epirubicin and Methotrexate Reported in VigiBase

Demographic Characteristics, n (%)	**Doxorubicin (N=79319)**	**Epirubicin (N=20007)**	**Methotrexate (N= 84992)**
Age group			
0-27days	52 (0.07)	23 (0.11)	13 (0.02)
28days-23months	223 (0.28)	9 (0.04)	211 (0.25)
2-11years	1926 (2.43)	74 (0.37)	2827 (3.33)
12-17years	1783 (2.25)	56 (0.28)	2062 (2.43)
18-44years	14356 (18.10)	3981 (19.90)	10332 (12.16)
45-64years	30234 (38.12)	10424 (52.10)	25118 (29.55)
65-74years	10073 (12.70)	2814 (14.07)	12052 (14.18)
≥75years	3650 (4.60)	573 (2.86)	6034 (7.10)
Unknown	17022 (21.46)	2053 (10.26)	26343 (30.99)
Gender			
Female	51277 (64.65)	16848 (84.21)	56738 (66.76)
Male	19363 (24.41)	2436 (12.18)	22205 (26.13)
Unknown	8679 (10.94)	723 (3.61)	6049 (7.12)
Continent			
Africa	736 (0.93)	110 (0.55)	477 (0.56)
Americas	25583 (32.25)	1426 (7.13)	51444 (60.53)
Asia	34499 (43.49)	9743 (48.70)	14504 (17.07)
Europe	17332 (21.85)	8554 (42.76)	18134 (21.34)
Oceania	1169 (1.47)	174 (0.87)	433 (0.51)
Notifier	**N=81766**	**N=20275**	**N=87597**
Physician	35899 (43.90)	7659 (37.78)	39447 (45.03)
Pharmacist	5544 (6.78)	1286 (6.34)	4632 (5.29)
Other Health Professional	20517 (25.09)	3898 (19.23)	24557 (28.03)
Lawyer	131 (0.16)	79 (0.39)	64 (0.07)
Consumer/Non-Health Professional	10266 (12.56)	801 (3.95)	15815 (18.05)
Unknown/blank	9409 (11.51)	6552 (32.32)	3082 (3.52)

3.3 System Organ Categories According to Continents

This section provides the top 10 ADRs reported from each continent according to the MedDRA system organ classification (SOC).

3.3.1 Top 10 System Organ Classes for Doxorubicin Based on Continents

Table 3.2 shows the top 10 ADRs (MedDRA SOCs) reported for doxorubicin from each continent. The top category in Africa and Asia was gastrointestinal disorder (16.86%; 23.86%), while the highest category reported from Oceania and Americas was general disorder and administration site condition (15.44%; 13.44%). Europe reported the highest for blood and lymphatic system disorders (17.21%).

Table 3.2 Top 10 System Organ Categories Reported for Doxorubicin Based on Continents

Continent	**System Organ Class**	**Frequency (%)**
Africa (N=1405)	Gastrointestinal disorders	237 (16.86)
	Blood and lymphatic system disorders	210 (14.95)
	Injury, poisoning, and procedural complications	159 (11.32)
	Skin and subcutaneous tissue disorders	159 (11.32)
	General disorders and administration site conditions	144 (10.25)
	Nervous system disorders	112 (7.97)
	Investigations	59 (4.20)
	Respiratory, thoracic, and mediastinal disorders	50 (3.56)
	Infections and infestations	46 (3.27)
	Cardiac disorders	37 (2.63)
Americas (N=83203)	General disorders and administration site conditions	11181 (13.44)
	Blood and lymphatic system disorders	8644 (10.39)
	Gastrointestinal disorders	8327 (10.01)
	Infections and infestations	7371 (8.86)
	Investigations	6609 (7.94)
	Respiratory, thoracic, and mediastinal disorders	6181 (7.43)
	Neoplasms benign, malignant, and unspecified	4962 (5.96)
	Nervous system disorders	4338 (5.21)

	Cardiac disorders	4122 (4.95)
	Injury, poisoning, and procedural complications	3895 (4.68)
Asia (N=60289)	Gastrointestinal disorders	14385 (23.86)
	Blood and lymphatic system disorders	12333 (20.46)
	Skin and subcutaneous tissue disorders	8083 (13.41)
	General disorders and administration site conditions	5052 (8.38)
	Nervous system disorders	3762 (6.24)
	Investigations	3181 (5.28)
	Musculoskeletal and connective tissue disorders	2448 (4.06)
	Metabolism and nutrition disorders	2324 (3.85)
	Respiratory, thoracic, and mediastinal disorders	1666 (2.76)
	Infections and infestations	1578 (2.62)
Europe (N= 40549)	Blood and lymphatic system disorders	6978 (17.21)
	General disorders and administration site conditions	5549 (13.69)
	Gastrointestinal disorders	3836 (9.46)
	Infections and infestations	3650 (9.00)
	Skin and subcutaneous tissue disorders	2684 (6.62)
	Respiratory, thoracic, and mediastinal disorders	2335 (5.76)
	Neoplasms benign, malignant, and unspecified	2242 (5.53)
	Cardiac disorders	2182 (5.38)
	Nervous system disorders	2006 (4.95)
	Investigations	1738 (4.29)
Oceania (N=2831)	General disorders and administration site conditions	437 (15.44)
	Blood and lymphatic system disorders	345 (12.19)
	Respiratory, thoracic, and mediastinal disorders	259 (9.15)
	Gastrointestinal disorders	242 (8.55)
	Infections and infestations	223 (7.88)
	Skin and subcutaneous tissue disorders	219 (7.74)
	Nervous system disorders	147 (5.19)
	Cardiac disorders	142 (5.02)
	Neoplasms benign, malignant, and unspecified	132 (4.66)
	Vascular disorders	123 (4.34)

3.3.2 Top 10 System Organ Classes for Epirubicin Based on Continents

Table 3.3 shows the top 10 ADRs (MedDRA SOCs) reported for epirubicin from each continent of the world. The highest category in Asia and Europe was blood and lymphatic system disorder (33.46%; 22.15%), while the top category reported from Oceania and Americas was general disorder and administration site condition (16.11%; 14.65%). The predominant class reported from Africa was gastrointestinal disorder (21.14%).

Table 3.3 Top 10 System Organ Categories Reported for Epirubicin Based on Continents

Continent	**System Organ Class**	**Frequency (%)**
Africa (N=246)	Gastrointestinal disorders	52 (21.14)
	Blood and lymphatic system disorders	40 (16.26)
	General disorders and administration site conditions	29 (11.79)
	Injury, poisoning, and procedural complications	25 (10.16)
	Investigations	18 (7.32)
	Skin and subcutaneous tissue disorders	17 (6.91)
	Nervous system disorders	11 (4.47)
	Hepatobiliary disorders	9 (3.66)
	Neoplasms benign, malignant, and unspecified	9 (3.66)
	Renal and urinary disorders	5 (2.03)
Americas (N=4922)	General disorders and administration site conditions	721 (14.65)
	Gastrointestinal disorders	649 (13.19)
	Blood and lymphatic system disorders	524 (10.65)
	Investigations	485 (9.85)
	Infections and infestations	348 (7.07)
	Respiratory, thoracic, and mediastinal disorders	337 (6.85)
	Cardiac disorders	268 (5.44)
	Nervous system disorders	260 (5.82)
	Neoplasms benign, malignant, and unspecified	251 (5.10)
	Metabolism and nutrition disorders	204 (4.14)
Asia (N=15119)	Blood and lymphatic system disorders	5060 (33.46)
	Gastrointestinal disorders	2853 (18.87)
	Investigations	2193 (14.50

	Skin and subcutaneous tissue disorders	1358 (8.98)
	General disorders and administration site disorders	952 (6.30)
	Nervous system disorders	653 (4.32)
	Metabolism and nutrition disorders	406 (2.69)
	Hepatobiliary disorders	296 (1.96)
	Cardiac disorders	271 (1.79)
	Respiratory, thoracic, and mediastinal disorders	173 (1.14)
Europe (N=18229)	Blood and lymphatic system disorders	4038 (22.15)
	General disorders and administration site conditions	2680 (14.70)
	Gastrointestinal disorders	2498 (13.70)
	Skin and subcutaneous tissue disorders	1149 (6.30)
	Infections and infestations	1118 (6.13)
	Cardiac disorders	941 (5.16)
	Respiratory, thoracic, and mediastinal disorders	861 (4.72)
	Nervous system disorders	827 (4.54)
	Neoplasms benign, malignant, and unspecified	803 (4.41)
	Vascular disorders	604 (3.31)
Oceania (N=391)	General disorders and administration site conditions	63 (16.11)
	Skin and subcutaneous tissue disorders	48 (12.28)
	Blood and lymphatic system disorders	35 (8.95)
	Gastrointestinal disorders	35 (8.95)
	Respiratory, thoracic, and mediastinal disorders	31 (7.93)
	Neoplasms benign, malignant, and unspecified	29 (7.42)
	Cardiac disorders	27 (6.91)
	Nervous system disorders	26 (6.65)
	Vascular disorders	22 (5.63)
	Infections and infestations	12 (3.07)

3.3.3 Top 10 System Organ Classes for Methotrexate Based on Continents

Table 3.4 shows the top 10 ADRs (MedDRA SOCs) reported for methotrexate from each continent. General disorder and administration site condition was the highest category across 4 continents (Africa- 16.01%; Americas- 32.32%; Europe- 15.54%; Oceania- 16.94%), while Asia reported neoplasms as the highest category (16.42%).

Table 3.4 Top 10 System Organ Categories Reported for Methotrexate Based on Continents

Continent	**System Organ Class**	**Frequency (%)**
Africa (N=937)	General disorders and administration site conditions	150 (16.01)
	Investigations	103 (10.99)
	Musculoskeletal and connective tissue disorders	102 (10.89)
	Gastrointestinal disorders	101 (10.78)
	Infections and infestations	64 (6.83)
	Skin and subcutaneous tissue disorders	58 (6.19)
	Blood and lymphatic system disorders	51 (5.44)
	Injury, poisoning, and procedural complications	51 (5.44)
	Metabolism and nutrition disorders	33 (3.52)
	Nervous system disorders	33 (3.52)
Americas (N=143807)	General disorders and administration site conditions	46481 (32.32)
	Gastrointestinal disorders	13930 (9.69)
	Musculoskeletal and connective tissue disorders	13915 (9.67)
	Infections and infestations	9985 (6.94)
	Investigations	8877 (6.17)
	Skin and subcutaneous tissue disorders	7922 (5.51)
	Injury, poisoning, and procedural complications	6182 (4.30)
	Nervous system disorders	6046 (4.20)
	Immune system disorders	5951 (4.14)
	Respiratory, thoracic, and mediastinal disorders	5710 (3.97)
Asia (N=21727)	Neoplasms benign, malignant, and unspecified	3567 (16.42)
	Blood and lymphatic system disorders	3465 (15.95)
	Gastrointestinal disorders	2787 (12.83)
	Infections and infestations	2235 (10.29)

	Investigations	2202 (10.13)
	General disorders and administration site conditions	1373 (6.32)
	Skin and subcutaneous tissue disorders	1151 (5.29)
	Hepatobiliary disorders	864 (3.98)
	Respiratory, thoracic and mediastinal disorders	827 (3.81)
	Nervous system disorders	783 (3.60)
Europe (N=42158)	General disorders and administration site condition	6550 (15.54)
	Gastrointestinal disorders	5359 (12.71)
	Infections and infestations	5350 (12.69)
	Injury, poisoning, and procedural complications	2801 (6.64)
	Blood and lymphatic system disorders	2540 (6.02)
	Investigations	2527 (5.99)
	Nervous system disorders	2424 (5.74)
	Skin and subcutaneous tissue disorders	2377 (5.64)
	Musculoskeletal and connective tissue disorders	2153 (5.11)
	Respiratory, thoracic, and mediastinal disorders	2042 (4.84)
Oceania (N=1505)	General disorders and administration site conditions	255 (16.94)
	Infections and infestations	206 (13.69)
	Gastrointestinal disorders	145 (9.63)
	Injury, poisoning, and procedural complications	123 (8.17)
	Blood and lymphatic system disorders	92 (6.11)
	Respiratory, thoracic, and mediastinal disorders	86 (5.71)
	Nervous system disorders	84 (5.58)
	Investigations	79 (5.24)
	Musculoskeletal and connective tissue disorders	76 (5.05)
	Skin and subcutaneous tissue disorders	67 (4.45)

3.4 Pearson Chi-Squared Tests

Table 3.5 shows the Pearson chi-squared tests results ($p<0.05$ considered statistically significant). The results show all p-values are less than 0.05. Hence, it is concluded that the variables are not independent of each other and there is a statistically significant association between demographic characteristics (age group, gender, and continent) and experiencing any of the top 10 ADRs for the three drugs.

Table 3.5: Pearson Chi-Squared Test for Association Between the Top 10 ADRs and Demographic Characteristics

Drugs	**Demographic characteristics**	**Pearson chi-squared value**	**df**	**p-value**
Doxorubicin	Gender	1600	9	.000
	Continent	6600	36	.000
	Age group	2400	63	.000
Epirubicin	Gender	234.0841	9	.000
	Continent	5700	36	.000
	Age group	346.8304	63	.000
Methotrexate	Gender	475.9444	9	.000
	Continent	8000	36	.000
	Age group	4000	63	.000

3.5 Binary Logistic Regression Analysis (Doxorubicin)

Table 3.6 shows the binary logistic regression analysis results with the ADR as the dependent variable and demographic characteristics (age group, gender, and continent) as the independent variables. The table summarizes the variables that showed statistically significant associations. Americas (OR: 4.34, 95% CI: 1.61-11.70), Asia (OR: 9.17, 95% CI: 3.41-24.66), and Europe (OR: 6.74, 95% CI: 2.50-18.18) were strongly associated with the likelihood of developing leukopenia. Additionally, Americas (OR: 3.86, 95% CI: 2.19-6.78), Europe (OR: 2.76, 95% CI: 1.57-4.86), Oceania (OR: 3.50, 95% CI: 1.85-6.60), and male gender (OR: 1.82, 95% CI: 1.68-1.97) showed a higher likelihood of having febrile neutropenia. The male gender was linked to a higher likelihood of having neutropenia (OR: 1.16, 95% CI: 1.08-1.24).

Table 3.6: Binary Logistic Regression Analysis Showing Association of Demographic Characteristics with the Top 10 ADRs for Doxorubicin

Demographics Characteristics	**Adverse Drug Reaction (MedDRA Preferred Term)**	**p-value**	**Odds ratio (95% CI)**
Continent			
Americas	Neutropenia	0.009	0.64 (0.47-0.90)
	Nausea	0.025	1.72 (1.07-2.76)
	Vomiting	0.000	0.33 (0.25-0.44)
	Leukopenia	0.004	4.34 (1.61-11.70)
	Alopecia	0.000	0.30 (0.20-0.45)
	Febrile neutropenia	0.000	3.86 (2.19-6.78)
	Pyrexia	0.003	2.02 (1.27-3.21)
Asia	Neutropenia	0.018	0.68 (0.49-0.94)
	Nausea	0.000	2.61 (1.63-4.18)
	Vomiting	0.000	0.48 (0.36-0.63)
	Leukopenia	0.000	9.17 (3.41-24.66)
	Alopecia	0.040	1.50 (1.02-2.20)
	Pyrexia	0.006	0.52 (0.33-0.83)
	Diarrhoea	0.001	0.47 (0.30-0.75)
Europe	Vomiting	0.000	0.24 (0.18-0.33)
	Leukopenia	0.000	6.74 (2.50-18.18)
	Alopecia	0.000	0.16 (0.11-0.25)
	Febrile neutropenia	0.000	2.76 (1.57-4.86)
	Pyrexia	0.000	2.30 (1.45- 3.65)
	Thrombocytopenia	0.037	1.98 (1.04-3.77)
Oceania	Nausea	0.004	2.27 (1.30-3.96)
	Vomiting	0.000	0.41 (0.27-0.63)
	Alopecia	0.000	0.13 (0.05-0.33)
	Febrile neutropenia	0.000	3.50 (1.85-6.60)
	Pyrexia	0.000	3.13 (1.84-5.30)

	Diarrhoea	0.013	0.38 (0.18-0.82)
Age group			
12-17 years	Nausea	0.028	2.40 (1.1-5.26)
18-44 years	Nausea	0.028	2.36 (1.1-5.09)
	Vomiting	0.003	0.52 (0.34-0.80)
45-64 years	Nausea	0.029	2.34 (1.09-5.04)
	Vomiting	0.000	0.37 (0.24-0.56)
65-74 years	Vomiting	0.000	0.28 (0.18-0.43)
	Thrombocytopenia	0.033	2.47 (1.08-5.65)
Gender			
Male	Neutropenia	0.000	1.16 (1.08-1.24)
	Nausea	0.000	0.70 (0.65-0.75)
	Vomiting	0.000	0.84 (0.77-0.90)
	Leukopenia	0.008	0.90 (0.83-0.97)
	Alopecia	0.000	0.61 (0.56-0.67)
	Febrile neutropenia	0.000	1.82 (1.68-1.97)
	Pyrexia	0.000	1.31 (1.20-1.42)
	Anaemia	0.000	0.79 (0.72-0.87)
	Thrombocytopenia	0.000	2.18 (1.97-2.41)

3.6 Binary Logistic Regression Analysis (Epirubicin)

Table 3.7 shows the binary logistic regression analysis results with the ADR as the dependent variable and demographic characteristics (age group, gender, and continent) as the independent variables. The table summarizes the variables that showed statistically significant associations. Male gender (OR: 2.02, 95% CI: 1.76-2.30) and Asia (OR: 42.63, 95% CI%: 31.32-58.02) showed a higher likelihood of developing bone marrow failure. Additionally, ages 2-11 years showed 3.33 higher odds of having pyrexia (OR:3.33, 95% CI: 1.55-7.18) while the likelihood of having nausea was 59% higher in ages 18-44 years (OR:1.59, 95% CI: 1.33-1.90).

Table 3.7: Binary Logistic Regression Analysis Showing Association of Demographic Characteristics with the Top 10 ADRs for Epirubicin

Demographic Characteristics	**Adverse Drug Reaction (MedDRA Preferred Term)**	**p-value**	**Odds ratio (95% CI)**
Continent			
Asia	Bone marrow failure	0.000	42.63 (31.32-58.02)
	Vomiting	0.040	0.40 (0.16-0.96)
	Neutropenia	0.000	0.06 (0.02-0.15)
	Febrile neutropenia	0.006	0.13 (0.03-0.55)
Americas	Alopecia	0.036	0.24 (0.06-0.92)
	Agranulocytosis	0.000	0.05 (0.09-0.2)
Europe	White blood cell count decreased	0.000	0.03 (0.01-0.14)
	Agranulocytosis	0.000	0.09 (0.04-0.25)
Age group			
2-11 years	Pyrexia	0.002	3.33 (1.55-7.18)
18-44 years	Nausea	0.000	1.59 (1.33-1.90)
	White blood cell count decreased	0.008	0.78 (0.64-0.94)
45-64 years	Febrile neutropenia	0.000	0.64 (0.52-0.78)
Gender			
Male	Bone marrow failure	0.000	2.02 (1.76-2.30)
	Alopecia	0.000	0.48 (0.37-0.63)

3.7 Binary Logistic Regression Analysis (Methotrexate)

Table 3.8 shows the binary logistic regression analysis results with the ADR as the dependent variable and demographic characteristics (age group, gender, and continent) as the independent variables. The table summarizes the variables that showed statistically significant associations. Asia (OR:6.25, 95% CI: 3.09-12.70) and Europe (OR:3.89, 95% CI:1.92-7.85) were strongly linked to a higher likelihood of developing nausea. The male gender showed a likelihood of having drug ineffective outcome (OR: 1.34, 95% CI: 1.27-1.42) and arthralgia (OR:1.15, 95% CI: 1.03-1.30). Furthermore, the likelihood of having therapeutic product effect incomplete was 29% higher in males (OR:1.29, 95% CI: 1.16-1.42) and 17% higher in the age group 45-64 years (OR:1.17, 95% CI: 1.06-1.29). Additionally, ages 2-11 years showed a 66% decrease in odds (OR:0.34, 95%

CI: 0.15-0.79), and ages 12-17 years showed a 59% decrease in odds (OR:0.41, 95% CI: 0.20-0.84) of having therapeutic product effect incomplete.

Table 3.8: Binary Logistic Regression Analysis Showing Association of Demographic Characteristics with the Top 10 ADRs for Methotrexate

Demographic Characteristics	**Adverse Drug Reaction (MedDRA Preferred Term)**	**p-value**	**Odds ratio (95% CI)**
Continent			
Americas	Arthralgia	0.000	0.32 (0.17-0.59)
	Vomiting	0.000	0.11 (0.07-0.20)
Asia	Drug ineffective	0.000	0.09 (0.05-0.16)
	Nausea	0.000	6.25 (3.09-12.70)
	Drug intolerance	0.002	0.11 (0.03-0.44)
	Fatigue	0.031	0.38 (0.16-0.91)
	Arthralgia	0.000	0.20 (0.10-0.41)
	Treatment failure	0.000	0.04 (0.01-0.18)
Europe	Drug ineffective	0.005	0.49 (0.30-0.80)
	Nausea	0.000	3.89 (1.92-7.85)
	Arthralgia	0.001	0.35 (0.18-0.65)
	Vomiting	0.004	0.44 (0.25-0.77)
	Treatment failure	0.007	0.24 (0.08-0.68)
Oceania	Vomiting	0.033	0.39 (0.16-0.93)
Age group			
2-11 years	Therapeutic product effect incomplete	0.011	0.34 (0.15-0.79)
	Alopecia	0.000	0.20 (0.09-0.43)
12-17 years	Therapeutic product effect incomplete	0.014	0.41 (0.20-0.84)
	Alopecia	0.033	0.58 (0.35-0.96)
45-64 years	Therapeutic product effect incomplete	0.002	1.17 (1.06-1.29)
	Vomiting	0.000	0.14 (0.06-0.31)
65-74 years	Vomiting	0.000	0.12 (0.05-0.27)
Gender			
Male	Drug ineffective	0.000	1.34 (1.27-1.42)
	Nausea	0.003	0.88 (0.81-0.96)

	Drug hypersensitivity	0.000	0.70 (0.64-0.78)
	Drug intolerance	0.004	0.86 (0.77-0.95)
	Therapeutic product effect incomplete	0.000	1.29 (1.16-1.42)
	Alopecia	0.000	0.17 (0.13-0.21)
	Arthralgia	0.017	1.15 (1.03-1.30)

3.8 Comparison between ADRs for Doxorubicin from VigiBase and Drug Package Insert

This section provides the results from comparison between the top 50 ADRs (MedDRA PT) for doxorubicin identified in this study and ADRs on the 3 drug package inserts (PIs) on the SAHPRA website (Caelyx®, Rubexet, Cipla Doxorubicin). The findings reveal that certain ADRs are not on the PIs. The ADRs that are not labeled on the PIs are highlighted in table 3.9. The main findings were disease progression, off-label use, and product use in unapproved indication.

Table 3.9: Top 50 ADRs Reported for Doxorubicin in VigiBase Compared with Drug Package Insert

Drug Package Insert	**VigiBase**
Blood and lymphatic system disorders Leukopenia, anaemia, thrombocytopenia, haemorrhage, neutropenia, febrile neutropenia, bone marrow suppression	Neutropenia, leukopenia, anaemia, thrombocytopenia, febrile neutropenia, bone marrow failure, pancytopenia
Immune system disorders Anaphylaxis, allergic reactions/hypersensitivity	++
Nervous system disorders Headache, dizziness, peripheral neuropathy, somnolence, lethargy, paresthesia, hypertonia, dysgeusia, syncope	Dizziness, neuropathy peripheral, headache
Eye disorders Conjunctivitis, keratitis, lacrimation, blurred vision	++
Cardiac disorders Dysrhythmias, congestive heart failure, sinus tachycardia, atrioventricular and bundle branch block, asymptomatic reductions in left ventricular ejection fraction, cardiomyopathy	Cardiac failure, cardiomyopathy
Vascular disorders	

Hypotension, phlebitis, thrombophlebitis, thromboembolism, hot flushes, vasodilation, hypertension	Hypotension
Respiratory, thoracic, and mediastinal disorders Bronchospasm, radiation pneumonitis, dyspnoea, cough	Dyspnoea, cough
Gastrointestinal disorders Nausea, vomiting, stomatitis, mucositis, anorexia, diarrhoea, oesophagitis, abdominal pain, dehydration, flatulence gastric erosions, gastrointestinal bleeding, hyperpigmentation of the oral mucosa, colitis, and gastrointestinal ulceration	Nausea, vomiting, diarrhea, constipation, abdominal pain, stomatitis
Hepatobiliary disorders Changes in transaminase levels	++
Skin and subcutaneous tissue disorders Alopecia, skin changes, itch, skin and nail hyperpigmentation, rash, radiation recall reactions (inflammatory reactions in irradiated skin), photosensitivity urticaria, acral erythema, palmar-plantar erythrodysesthesia syndrome	Alopecia, palmar-plantar erythrodysesthesia syndrome, rash, pruritus, erythema
Renal and urinary disorders Urine discolouration	++
Reproductive system and breast disorders Amenorrhoea, oligospermia, azoospermia	++
General disorders and administration site conditions Fever, malaise, asthenia, chills, shock, local toxicity, extravasation, cellulitis, or tissue necrosis at the injection site, phlebosclerosis	Pyrexia, asthenia, fatigue, death, pain, **disease progression**, oedema peripheral, chest pain, injection site reaction, chills, mucosal inflammation
Investigations ECG abnormalities, increased aspartate aminotransferase, decreased ejection fraction, increased blood creatinine, increased alanine aminotransferase, decreased blood cell count	White blood cell count decreased, neutrophil count decreased, platelet count decreased
Infections and Infestations Infection, sepsis, septicaemia, pneumonia	Pneumonia, sepsis, infection
Metabolism and nutrition disorders	Decreased appetite, dehydration

Hyperuricaemia, anorexia, hypokalemia, hyperkalemia, hypomagnesaemia, hyponatraemia, hypocalcaemia, decreased appetite, dehydration	
Neoplasms benign, malignant and unspecified Acute lymphocytic leukaemia, acute myelogenous leukaemia	Acute myeloid leukaemia
Injury, poisoning and procedural complications -	**Off-label use**, **product use in unapproved indication**
Musculoskeletal and connective tissue disorders Leg cramps, bone pain, back pain, myalgia, pain in extremity, arthralgia, muscle weakness	Myalgia, back pain

++ = not reported in VigiBase

3.9 Comparison between ADRs for Epirubicin from VigiBase and Drug Package Insert

This section provides results from comparison between the top 50 ADRs (MedDRA PT) identified in this study for epirubicin and ADRs on the two drug package inserts on the SAHPRA website (Aspen Epirubicin, Farmorubicin). The findings reveal some ADRs were not labeled on the PIs. The ADRs that are not mentioned in the PIs are highlighted in table 3.10. The main findings were pneumonia, constipation, decreased appetite, pulmonary embolism, pain, chest pain, pain in the extremity, dizziness, dysgeusia, paraesthesia.

Table 3.10: Top 50 ADRs Reported for Epirubicin in VigiBase Compared with Drug Package Insert

Drug Package Insert	**VigiBase**
Blood and lymphatic system disorders Leukopenia, neutropenia, anaemia, thrombocytopenia, bleeding	Bone marrow failure, leukopenia, anaemia, neutropenia, agranulocytosis, febrile neutropenia, pancytopenia, thrombocytopenia, granulocytopenia
Infection and infestations Infection	**Pneumonia**, infection, sepsis
Cardiac disorders Congestive heart failure (CHF), symptomatic drop in left ejection fraction (LVEF), arrhythmias	Cardiac failure, cardiomyopathy

Gastrointestinal disorders Nausea, vomiting, mucositis, stomatitis, diarrhea, pain or burning sensation, erythema, dehydration, erosions, ulceration, gastrointestinal bleeding, hyperpigmentation of oral mucosa	Nausea, vomiting, diarrhea, **constipation**, stomatitis, abdominal pain, mouth ulceration
Metabolism and nutrition disorders Anorexia, Dehydration	**Decreased appetite**, dehydration
Skin and subcutaneous tissue disorders Alopecia, local toxicity, rash/, /itch, skin changes, pain or burning sensation, erythema, dehydration Flushes, skin and nail hyperpigmentation, hypersensitivity to irradiated skin (radiation recall reaction), photosensitivity, urticaria	Alopecia, rash, nail discolouration, erythema, pruritus
Respiratory, thoracic and mediastinal disorders Dyspnoea, cough	Dyspneoa, **pulmonary embolism**, cough
General disorders and administration site conditions Malaise, asthenia, fever, mucositis, death	Pyrexia, asthenia, fatigue, mucosal inflammation, **pain**, malaise, **chest pain**, death, general physical health deterioration
Reproductive system and breast disorders Amenorrhoea	++
Renal and Urinary disorders Red colouration of urine 1-2 days after administration, acute renal failure, nephrotoxicity	++
Nervous system disorders Headache	Headache, **dizziness**, **dysgeusia**, **paraesthesia**
Hepatobiliary disorders Hepatic function abnormal (changes in transaminase levels)	Hepatic function abnormal
Investigations Changes in transaminase levels, abnormal blood cell count	Ejection fraction decreased, white blood cell count decreased, neutrophil count decreased
Eye disorders	

Conjunctivitis/keratitis, increased lacrimation	++
Neoplasms benign, malignant, and unspecified Acute lymphocytic leukaemia, acute myelogenous leukaemia	Acute myeloid leukaemia
Immune system disorders Anaphylaxis	++
Vascular disorders Hot flushes, phlebitis, thrombophlebitis, thromboembolism, shock, hypotension	++
Musculoskeletal and connective tissue disorders -	**Pain in extremity**

++ = not reported in VigiBase

3.10 Comparison between ADRs for Methotrexate from VigiBase and Drug Package Insert

This section provides results from the comparison between the top 50 ADRs (MedDRA Preferred Terms) for methotrexate identified in this study and ADRs on the drug package insert on the SAHPRA website (Abitrexate®). The findings show that certain ADRs are not labeled on the PIs. The ADRs that are not mentioned on the PIs are highlighted in table 3.11. The main findings were drug ineffective, drug intolerance, therapeutic product effect incomplete, therapeutic product effect decreased, treatment failure, condition aggravated, off-label use, product use in unapproved indication.

Table 3.11: Top 50 ADRs Reported for Methotrexate in VigiBase Compared with Drug Package Insert

Drug Package Insert	**VigiBase**
Blood and lymphatic system disorders Anaemia, leukopenia, thrombocytopenia, myelosuppression, granulocytopenia, pancytopenia, agranulocytosis	Leukopenia, pancytopenia, bone marrow failure, neutropenia, thrombocytopenia, febrile neutropenia, anaemia, lymphoproliferative disorder
Infection and infestations	Pneumonia, infection, nasopharyngitis, interstitial lung disease

Opportunistic infections, respiratory or cutaneous bacterial infection, pneumonia, interstitial lung disease, herpes zoster, sepsis/ neutropenic sepsis	
Gastrointestinal disorders Pharyngitis, stomatitis, gingivitis, nausea, vomiting, anorexia, diarrhoea, hematemesis, melena, gastrointestinal ulceration and haemorrhage, loss of appetite, mucositis, enteritis	Nausea, vomiting, diarrhoea, abdominal discomfort, abdominal pain, gastrointestinal disorder, stomatitis, mouth ulceration
Metabolism and nutrition disorders Diabetes, dehydration	++
Skin and subcutaneous tissue disorders Pruritus, erythema, alopecia, urticaria, photosensitivity, furunculosis, depigmentation, ecchymosis, acne, toxic epidermal necrolysis, telangiectasia, Steven Johnson rash, psoriatic lesions	Alopecia, rash, pruritus, psoriasis
Respiratory, thoracic, and mediastinal disorders Interstitial pneumonitis, chronic interstitial obstructive lung disease with symptoms of cough, dyspnoea, fever, hypoxemia, and infiltration in lung radiography	Dyspnoea, cough
General disorders and administration site conditions Fatigue, malaise, chills, fever, reduced resistance to diseases, sudden death, oedema	**Drug ineffective**, **drug intolerance**, **therapeutic product effect incomplete**, **therapeutic product effect decreased**, fatigue, pain, **treatment failure**, malaise, **condition aggravated**, pyrexia, asthenia, peripheral swelling
Reproductive system and breast disorders Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, infertility, abortion, teratogenic effects, foetal deviations, loss of libido, impotence	++
Renal and Urinary disorders Nephropathy or renal insufficiency, azotemia, cystitis, hematuria	++
Nervous System Disorders Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and convulsions, chemical arachnoiditis, leukoencephalopathy, transient acute neurological syndrome, dizziness	Headache, dizziness

Hepatobiliary disorders Acute (increase in transaminases) or chronic (fibrosis and cirrhosis) hepatotoxicity	++
Investigations Increase in transaminases	Hepatic enzymes increased, liver function test increased
Neoplasms benign, malignant, and unspecified Lymphomas	Lymphoma
Immune system disorders Hypogammaglobulinemia, anaphylaxis	Drug hypersensitivity
Vascular disorders Vasculitis, hypotension, thromboembolic events	++
Injury, poisoning, and procedural complications Increased risk of toxic reactions (soft tissue necrosis, osteonecrosis)	**Off-label use**, **product use in unapproved indication**
Musculoskeletal and connective tissue disorders **A**rthralgia/myalgia, osteoporosis	Arthralgia, rheumatoid arthritis, joint swelling, pain in extremity, musculoskeletal stiffness
Eye disorders Conjunctivitis, blurred vision, retinopathy	++
Cardiac disorders Myocardial ischemia, pericardial effusion	++

++ = not reported in VigiBase

CHAPTER 4

DISCUSSION

4.1 Introduction

Chemotherapy is a mainstay of many clinical protocols for treating cancers locally and globally (Cheng *et al.,* 2020). However, anti-cancer drugs are prone to cause ADRs, limiting their use (Ghandi *et al.,* 2005). Although common ADRs following chemotherapy administration are documented in the literature, no study has assessed ADRs for specific cancer drugs from a global safety database. This study has provided valuable results on the patterns of ADRs for three commonly prescribed chemotherapy drugs; doxorubicin, epirubicin, and methotrexate. This chapter will discuss the results provided in this study in the light of previous studies.

4.2 Demographic Data

Of the 184,318 ICSRs analyzed, majority of the reports were from females (Dox= 64.65%; Epi= 84.21%; Met= 66.76%) while less than one-third were from males (Dox=24.41%; Epi=12.18%; Met= 26.13%) (Table 3.1). Globally, several study findings demonstrate that females have a higher vulnerability to ADRs than males (Rademaker, 2001). Results from a survey involving ten prescription drugs withdrawn from the United States market indicated that eight of the ten drugs posed greater risks of adverse effects in women than men (United States General Accounting Office, 2001). Also, a prospective observational study on chemotherapy-induced ADRs in oncology patients reported 73.6% ADRs in females (Chopra *et al.*, 2016). These findings may be attributed to gender-wise differences that influence drug pharmacokinetics and subsequent toxicity (Soldin, Chung and Mattison, 2011). For instance, due to variations in the expression of metabolic enzymes in the liver (CYP3A4), chemotherapy drugs tend to have a longer drug half-life and a higher risk of toxicity in female patients than in males (Parkinson *et al*., 2004). Other essential factors include absorption, conjugation, renal elimination, and protein binding, which may also have gender-based variations (Rademaker, 2001). Furthermore, studies indicate that females

generally possess better healthcare-seeking attitudes than males. Hence, females are more likely to report an ADR (Thompson *et al*., 2016).

Most of the ADR reports occurred between 18-74 years, with 45-64 years being the predominant age group (Dox=38.12%, Epi=52.10%; Met=29.55%) (Table 3.1). This finding is consistent with the literature, which shows that the prevalence of ADRs increases with age (Jose and Rao, 2006; Mallik *et al*., 2007; Poddar *et al.*, 2009; Prasad *et al.*, 2013). This may suggest a general decline in system organ capacity leading to low metabolizing capacity and reduced excretion. Consequently, this results in drug accumulation in the body, increasing the risk of toxicities (Bates, Leape and Carruthers, 2000). Hence, healthcare professionals should take additional precautions while administering chemotherapy drugs to geriatric patients.

Regarding continental data, Asia recorded the highest reports for doxorubicin and epirubicin (Dox= 43.49%; Epi= 48.70%), whereas Americas had the highest reports for methotrexate (Met= 60.53%) (Table 3.1). This finding may reflect differences in drug utilization patterns and policies across various continents of the world. For instance, Asia records almost half of the new cancer cases and more than 50% of the cancer mortality globally, indicating a high consumption of cancer chemotherapy which may reflect more ADRs (Eniu *et al*., 2019). Also, the Pan-Asia has adapted the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the treatment of breast cancer, which uses cyclophosphamide, epirubicin and fluorouracil (CEF), and cyclophosphamide, doxorubicin and fluorouracil (CAF) (Park *et al.*, 2020). This indicates high consumption of anthracyclines which may reflect the high ADR reports of the drugs recorded in Asia (Park *et al.*, 2020).

Africa and Oceania generally showed the least reporting (Dox=0.93%; Epi=0.55%; Met=0.51%) compared to other continents. This finding is in keeping with the literature, and it may depict the state of the health systems. As highlighted by Isah *et al.* (2012), PV systems in Africa are essentially weak and lack resources and infrastructure compared to developed countries. A global analysis conducted by Aagaard *et al.* (2012) found that high-income countries generally reported higher PV than low-income countries. While anti-neoplastic drugs constituted most of the reports from high-income countries, low-income countries such as Africa reported more ADRs for anti-

infectives (Aagaard *et al*., 2012). In line with past studies, the findings from this study reflect a PV system in Africa that is not robust and only focuses on prevailing conditions such as communicable diseases. Therefore, efforts should be made to provide the resources and infrastructure needed to make PV more robust and extensive in the African setting.

Physicians were the predominant reporters in this study (Dox=43.90%; Epi=37.78%; Met= 45.03%) (Table 3.1). These findings may be because only physician reporting was allowed for many years after the initiation of the WHO programme for international drug monitoring in the 1960s (Blenkinsopp *et al.*, 2007). Only a few countries like the USA and Sweden allowed non-physician reports, and reports from patients or other healthcare professionals were only incorporated over time (Van Grootheest, de Graaf and de Jong-van den Berg, 2003; Blenkinsopp *et al*., 2007; Aagaard, Nielsen and Hansen, 2009). To date, many countries have still not integrated consumer reporting into their national PV programme.

A significant proportion of the demographic data; age group (Dox=21.46; Epi=10.26; Met=30.99) and gender (Dox=10.94%; Epi=3.61%; Met=7.12%) was reported as unknown (Table 3.1). Also, some reports (Dox=11.51%; Epi=32.32%; Met=3.52%) missed out on the notifier's qualification even though this is part of the WHO minimum requirements for an ICSR to be considered valid (UMC, 2012). These findings may reflect an inadequate knowledge of how to properly fill the ADR forms, or time constraints when documenting the ADRs. Healthcare professionals should be adequately trained on the reporting requirements to improve the quality of the global safety data.

4.3 Top 10 System Organ Categories According to Continents

This study revealed the top 10 SOCs reported from each of the world's five continents. The predominant categories reported for doxorubicin from the continents were gastrointestinal disorders (Africa=16.86%; Asia=23.86%), general disorders and administration site conditions (Oceania=15.44%; Americas=13.44%), and blood and lymphatic system disorders (Europe=17.21%) (Tables 3.2). This is in keeping with past literature, which showed that gastrointestinal issues (nausea, vomiting, mucositis) and myelosuppression are common in patients using doxorubicin-based regimens (Fukuda *et al*., 2017; Johnson-Arbor and Dubey, 2021). Although typically considered non-lethal, gastrointestinal issues could significantly impair quality

of life and result in non-adherence or treatment discontinuation. This is crucial as non-adherence, and early discontinuation of chemotherapy have been identified as significant predictors of disease progression and mortality in patients with cancer (Hershman *et al.*, 2011). Hence, early interventions may be necessary to minimize or proactively manage these reactions in patients. Furthermore, blood system reactions are paramount in cancer chemotherapy due to the increased risk of life-threatening infections and complications due to decreased immunity (Nurgalieva, Liu and Du, 2011). Careful monitoring of blood counts is usually performed during therapy with doxorubicin, especially in easily predisposed or immunocompromised individuals such as patients with pre-existing HIV or tumours involving the bone marrow.

A noteworthy and important finding for doxorubicin was the reporting of injuries, poisoning, and procedural complications from Africa (n=159; 11.32%) (Table 3.2). These findings may suggest incorrect techniques of product administration or medication errors which could potentially have devastating consequences. This issue is critical in oncology due to the high risk of errors that could arise from dosage calculations or adjustment protocols and mixing procedures. A review of published literature from 1980 to 2017 showed that chemotherapy errors happen at a rate of one to four per 1000 prescriptions, affect about 1–3% of paediatric and geriatric patients, and occur at all phases of the medication use process (Weingart *et al*., 2018). Certain chemotherapy drugs such as anthracyclines have been identified to present with a high risk of errors (Weingart *et al*., 2018). A study from Swedish national reporting systems found doxorubicin to be one of the four most associated anti-cancer drugs with incorrect doses and drug errors (Fyhr and Akselsson, 2012). Of these errors, 42% occurred from prescribing, 42% while dispensing at pharmacies, and 8% during preparation by nurses (Fyhr and Akselsson, 2012)**.**

In the African healthcare setting, medication errors have been reported to be relatively common (Mekonnen, *et al*., 2018). A study reviewing medication errors in 9 African countries revealed that about 13% to 76% of errors occur in general medicine (Mekonnen, *et al*., 2018). Data on medication errors in chemotherapy in the African setting are scarce. However, a report from Uganda revealed a high incidence of medication errors (47.3%) among cancer patients (Dorothy, Yadesa and Atukunda, 2021). Of these errors, 37.18% were administration errors, 11.54% transcription errors, 42.31% prescription errors, and 8.97% dispensing errors (Dorothy, Yadesa

and Atukunda, 2021). Providing continuous training to healthcare professionals and developing safe practice standards may be critical steps in minimizing the potential for errors, especially in Africa.

Epirubicin is a derivative of doxorubicin, albeit a safer option (Khasraw, Bell and Dang, 2012). As such, it is expected to have comparable ADRs with doxorubicin. The ADR categories for epirubicin in this study were similar to doxorubicin. Blood and lymphatic system disorders (Asia=33.46%; Europe=22.15%), general disorders and administration site conditions (Oceania=16.11%; Americas=14.65%), and gastrointestinal disorders (Africa=21.14%) were the most common categories across the continents (Table 3.3). These findings, however, could not suggest if epirubicin is safer than doxorubicin since variations in patterns of drug use and reporting biases across different continents could have influenced reports for each drug.

The most predominant reports for methotrexate across continents were general disorders and administration site conditions (Africa=16.01%; Americas=32.32%; Europe=15.54%; Oceania=16.94%), except for Asia, which reported neoplasms as the top category (Asia=16.42%) (Table 3.4). Contrary to this finding, previous studies have documented gastrointestinal side effects as most prevalent, followed by liver toxicities such as transaminitis (Salliot and Van der Heijde, 2009; Albrecht and M ler-Ladner, 2010). Also, Gaies and colleagues (2012) reported blood and lymphatic, gastrointestinal mucosa, and hair cells as the most prevalent reactions secondary to their high rate of cellular turnover. While general disorders such as pain and fatigue are majorly self-limiting, administration site conditions like extravasations are common and could result in more serious complications like tissue necrosis. Thus, vigilant monitoring remains crucial, particularly during slow intravenous administration of methotrexate.

More than 1 in 10 reports of methotrexate-induced neoplasms were recorded in Asia (n=3567, 16.42%) (Table 3.4). The link between methotrexate and malignancy risk has been investigated in patients. However, the findings have been somewhat inconsistent (Mariette *et al.*, 2002; Buchbinder *et al*., 2008; Perng *et al*., 2020). A study conducted in Australia reported that patients using methotrexate had a 50% increased likelihood of developing any type of cancer, owing to its immunosuppressive effects (Buchbinder *et al*., 2008). A more recent Swedish study of 12,656

cases revealed no increase in the risk of having lymphoma among patients (Hellgren *et al*., 2017). Further, a 12-year retrospective study in Taiwan showed that middle and high cumulative doses might be associated with a lower likelihood of new cancer cases (Perng *et al*., 2020). From the literature, there is insufficient evidence regarding the association of neoplasms with methotrexate. Further studies may be needed to ascertain and characterize this risk, particularly within the Asian setting.

4.4 Logistic Regression Analysis

The binary logistic regression analysis for doxorubicin showed that Americas (OR: 4.34, 95% CI: 1.61-11.70), Asia (OR: 9.17, 95% CI: 3.41-24.66), and Europe (OR: 6.74, 95% CI: 2.50-18.18) were strongly associated with the likelihood of developing leukopenia (Table 3.6). The male gender was linked to a higher likelihood of having neutropenia (OR: 1.16, 95% CI: 1.08-1.24). Also, the likelihood of having febrile neutropenia was 82% higher in males (OR: 1.82, 95% CI: 1.68-1.97). Literature indicates that the male gender is linked to neutropenic conditions, which is consistent with this present study (Hsieh *et al*., 2007). A study in the United States determining the demographic differences relating to neutrophil counts found neutropenia to be associated with males and children younger than five years of age (Hsieh *et al*., 2007). Also, results from a retrospective study showed that males had prolonged hospital admission due to febrile neutropenia compared with females (Dulisse *et al*., 2013). Hence, it may be critical to take necessary precautions and proactively manage neutropenic reactions in males.

Analysis for epirubicin showed that the male gender (OR: 2.02, 95% CI: 1.76-2.30) and Asia (OR: 42.63, 95% CI%: 31.32-58.02) had a higher likelihood of developing bone marrow failure (Table 3.7). Further, the likelihood of having nausea was 59% higher in ages 18-44 years (OR:1.59, 95% CI: 1.33-1.90) while the age 2-11 years showed 3.33 higher odds of having pyrexia (OR:3.33, 95% CI: 1.55-7.18). This finding is in keeping with previous literature, which showed that baseline temperature is generally higher in children than in adults (Roghmann, Mackowiak and Warner, 2001; Peres *et al.*, 2004; Sessler, 2009). These findings may be due to thermoregulation mechanisms which are well preserved in the elderly resulting in lower baseline temperature, as highlighted by Sessler (2009).

Based on the analysis for methotrexate, Asia (OR:6.25, 95% CI: 3.09-12.70) and Europe (OR:3.89, 95% CI:1.92-7.85) were strongly linked to a higher likelihood of developing nausea (Table 3.8). Also, males showed a likelihood of having drug ineffective outcomes (OR: 1.34, 95% CI: 1.27-1.42) and arthralgia (OR:1.15, 95% CI: 1.03-1.30). The likelihood of having a therapeutic product effect incomplete was 29% higher in males (OR:1.29, 95% CI: 1.16-1.42) and 17% higher in the age group 45-64 years (OR:1.17, 95% CI: 1.06-1.29). On the other hand, ages 2-11 years showed a 66% decrease in odds (OR:0.34, 95% CI: 0.15-0.79), and ages 12-17 years showed a 59% decrease in odds (OR:0.41, 95% CI: 0.20-0.84) of having therapeutic product effect incomplete. These findings show that therapeutic or drug-ineffective issues are associated with the male gender and the elderly population. Elderly patients are more likely to experience metabolic changes and decreased drug clearance which could affect therapeutic outcomes (Bates, Leape and Carruthers, 2000). Moreover, polypharmacy is more pronounced in geriatric patients and can result in non-adherence and lower therapeutic outcomes (Kurczewska-Michalak *et al*., 2021).

4.5 Comparison between the Top 50 ADRs from VigiBase and Drug Package Inserts

Drug package inserts provide evidence-based information from clinical trials and post-marketing surveillance approved by regulatory authorities (Shivkar, 2009). It is an important tool that provides physicians with a reliable framework to prescribe and dispense medicines for safe and effective use.

A comparison of the South African approved package inserts with the top 50 ADRs in this study revealed some ADRs were missing for doxorubicin: disease progression, off-label use, and product use in unapproved indication (Table 3.9). Disease progression is an adverse event that may reflect non-adherence to doxorubicin owing to unbearable reactions. In a study conducted by McCowan and colleagues (2008), non-adherence to medication was closely linked with disease progression. Moreover, disease progression could result from other factors such as drug resistance, which may require combination chemotherapy or a complete change in cancer therapy (Byler *et al.*, 2014; Housman *et al.*, 2014).

The practice of "off-label use" and "product use in unapproved indication" for doxorubicin is in keeping with the literature (Hamel *et al*., 2015; Eaton, Sima and Panageas, 2016). While the latter

term denotes drug use only outside approved indications, off-label use covers broader terms such as use in unapproved indications, unapproved route of administration, unapproved doses, or a special population (Neubert *et al*., 2008). In the literature, the off-label use of doxorubicin includes the management of metastatic hepatocellular cancer, advanced endometrial carcinoma, advanced renal cell carcinoma, and multiple myeloma (Douedi and Carson, 2020). Although this practice may sometimes be clinically justified in oncology, a major drawback is a concern about patient safety, especially for drugs that have a high potential for toxicity, like chemotherapy drugs. In a study conducted in Italy, off-label use significantly increased the risk of serious ADRs in patients (Viola *et al.*, 2016). Further studies may be required to re-evaluate the off-label use of doxorubicin, its harms and benefits, and regulatory actions should be taken where necessary.

On reviewing the PIs for epirubicin, pneumonia was not listed as one of the adverse reactions (Table 3.10). Although the PIs examined indicated the possibility of occurrence of infections, pneumonia is not precisely stated. Pneumonia is an important reaction in oncology which is estimated to cause or complicate almost 10% of hospital admissions among cancer patients (Garcia *et al.*, 2013; Gonzalez *et al*., 2014; Evans and Ost, 2015). A few studies have suggested a link between epirubicin and pneumonia. For instance, Wijaya et *al*. (2017) observed a high incidence of *pneumocystis jirovecii* pneumonia (PCP) in advanced breast cancer patients receiving weekly epirubicin-based therapy. Also, recently, during the evaluation of serious adverse event reports, the Korean Institute of Drug Safety (KIDS) found a causal association between epirubicin and *pneumocystis jirovecii* pneumonia (PCP) (WHO, 2019). This discovery led the Ministry of Food and Drug Safety, the regulatory body in Korea, to update the drug label (Pharmorubicin®) to include pneumonia as an ADR (WHO, 2019). Therefore, physicians in South Africa should be aware that pneumonia could develop during treatment with epirubicin and should counsel patients and report new cases. Furthermore, nervous system reactions (dizziness, dysgeusia, paraesthesia) were missing on the PIs for epirubicin. Dizziness and paraesthesia have been linked to epirubicin and are labeled as potential side effects in the Australia epirubicin package insert (Pharmorubicin®) (TGA, 2021). Nonetheless, there might be a need to investigate these reactions further and update the PIs in South Africa to alert healthcare professionals.

The majority of the missing ADRs for methotrexate were drug-related issues such as “drug ineffective” or “therapeutic product effect incomplete” and poor therapeutic outcomes (treatment failure) (Table 3.11). These findings may signal a wide range of issues from drug-related problems like product quality factors, to subjective patient factors such as non-adherence or healthcare system factors like medication errors.

Medication errors and dosage issues have been identified in the literature as major events relating to methotrexate use (Boyd, 2002; Moore, Walsh and Cohen, 2004; Cairns *et al.*, 2016). Previously, spontaneous reporting by healthcare professionals in Australia had uncovered a significant number of dosage problems relating to methotrexate use (Boyd, 2002). Additionally, a link between medication errors and methotrexate was reported in Ireland which led to the update of drug package inserts (HPRA, 2019). An assessment of medication errors involving methotrexate in the United States showed that errors exist during all stages of the medication use process (Moore, Walsh and Cohen, 2004). The most common type of error was often a result of uncertainty about the once-weekly dosage schedule (30%), and errors often led to death (24%) or other serious adverse reactions (45%) (Moore, Walsh and Cohen, 2004). Other typical errors reported with methotrexate include overdoses due to the variation of doses for different diseases (Swanepoel, 2013). For instance, a normal dosage of methotrexate can range from 10 to 20,000 mg (Swanepoel, 2013). While overdosage is likely to result in serious damage to patients, under dosage may compromise the success of therapy. It is pertinent to note that the PI on the SAHPRA website carries an important boxed warning about dosage errors specifically for the “once weekly” treatment of rheumatoid arthritis and psoriasis. Nonetheless, it is crucial to investigate methotrexate dosage issues in oncology to improve patient outcomes and prevent potentially fatal consequences.

In South Africa, the PV advisory committee of the SAHPRA evaluates new safety concerns from PMS or other regulators and advises SAHPRA so that regulatory actions like package insert updates can be taken (Mehta *et al.*, 2017; SAHPRA, 2021). Afterward, the SAHPRA should notify the pharmaceutical company of regulatory decisions related to their suspected medicines. In addition, pharmaceutical companies are required to continuously update the information in the adverse reaction section of package inserts based on newly acquired information from PMS

(SAHPRA, 2021). The unlabelled ADRs highlighted in this study may reflect a shortcoming in the industry or a lack of collaboration between the regulatory body and pharmaceutical companies in South Africa. The inclusion of potential ADRs in approved PIs is vital to raise awareness among healthcare professionals and to advise patients.

4.6 Chapter Summary

This chapter gave a detailed discussion of the research findings from this study in the light of previous literature. The three oncology medicines were discussed in terms of their impact on organ systems with the top systems across continents highlighted. Further to this, the demographic associations with the top 10 ADRs were elaborated upon and the top 50 ADRs identified were discussed in relation to the South African package inserts. The following chapter provides recommendations from this study and the conclusion of the study.

CHAPTER 5

RECOMMENDATIONS AND CONCLUSION

5. 1 Introduction

This chapter concludes this dissertation by summarizing the findings of this study. The limitations of the study and the resultant recommendations are explained. In addition, the conclusions in relation to the research objectives and the implications of these findings are provided.

5.2 Limitations of the Study

The major strength of this global study is the use of VigiBase, involving diverse clinical settings and medical cultures over an extended period with a large sample of data. However, findings from this study may be limited by reporting bias due to differences in patterns of diseases, drug utilization, and health policies across various countries. It was also not possible to measure the magnitude of risk in VigiBase due to the significant under-reporting of cases. Additionally, the likelihood that the reported event was caused by the medicine varies from report to report. Some countries collect only suspected ADRs with a possible causal relationship between the drug and the reported reaction. In other countries, like the United States, which contributes almost 50% of the reports in VigiBase, suspected ADRs are just reported spontaneously without further checking to see if there is a link (UMC, 2018). Furthermore, due to the secondary nature of the study, there were missing details in the case reports. For instance, gender, age group, and continent variables were left blank or reported as unknown. In addition, there was limited clinical background information in the reports. For example, there was no information on existing patient co-morbidities or results from clinical investigations, and data on drug dosage was incompletely documented in the case reports. These data were not factored into this study and this may have hindered a comprehensive interpretation of ADR patterns in this study. Lastly, methotrexate is not solely used as an oncology medicine, and this study did not filter for relevance to patients treated for cancer only.

5.3 Future recommendations

Regulatory Actions for Missing ADRs on South Africa's Drug Package Inserts

An important finding of this study is that some ADRs reported in VigiBase are not labeled on the approved package inserts for South Africa. The SAHPRA should review these reported safety issues and update the package inserts accordingly. This is important so that healthcare professionals can be acquainted with the potential risks of the medications they prescribe and can advise patients appropriately. The SAHPRA should also consider package insert warning information where necessary as a means of minimizing potential adverse events from medication errors. Additionally, "dear doctor letters" from pharmaceutical industries approved by the SAHPRA may also help to alert healthcare professionals in South Africa on important medicine safety updates.

Development of Strategies to Prevent Medication Errors

Drug-related issues and poor therapeutic findings from this study may indicate ongoing harm resulting from methotrexate dosage errors. Globally, healthcare professionals, manufacturers, and regulatory entities need to put in efforts to reduce these risks. Emphasis should be placed on continuous training of healthcare professionals and developing safety protocols and guidelines to minimize the potential for errors. Also, strategies to minimize these events need to be evaluated and implemented. For instance, prescribers can include warning alerts for methotrexate during prescribing. Similarly, pharmacists can avoid dispensing unnecessarily large quantities of methotrexate and include warning alerts during dispensing to avoid dosage errors. Likewise, healthcare professionals should ensure to carefully counsel patients taking this drug for the first time or patients on discharge to minimize the risk of these errors. Since in this study methotrexate was not solely used as an anti-cancer medicine, additional studies may be required to assess medication errors relating to methotrexate in oncology settings.

Continuous Healthcare Professional Training on Pharmacovigilance

During analysis, a significant proportion of missing data was observed. These findings may reflect poor knowledge of healthcare professionals on the ADR reporting requirements. Future studies are recommended to investigate the reasons for incomplete filling of the ADR reporting forms in

healthcare settings. In the meantime, healthcare professionals should be continuously reminded and trained by the WHO on how to correctly fill the individual case safety report forms through conferences, workshops, and seminars. Pharmacovigilance training should be introduced during undergraduate studies and should continue as a regular training session in the workplace. This may improve the quality of the ICSRs submitted to the VigiBase and would strengthen subsequent PV studies.

Strategies to Improve ADR Reporting in Africa

The low number of reports from Africa in this study is an indication that ADR reactions are not adequately reported in healthcare settings. There is a dire need for government coordination and leadership to enable the continuous development and sustainability of PV in African member countries. Social media can also be viewed as a major stakeholder as its activities can serve to educate healthcare professionals and the public on the importance of ADR reporting. The government through the use of media publicity can encourage the use of free smartphone mobile apps such as the Med Safety app which allows direct ADR reporting to the national PV centres using a built-in support system. This may help minimize under-reporting and ease the voluntary reporting of ADRs by healthcare professionals and patients.

Recommendations for Future PV Studies

The findings from this study were primarily based on spontaneous reporting. Since spontaneous reporting alone cannot estimate the strength of association between the occurrence of an adverse reaction and the drug, future causality assessment studies are recommended. Further research should consider factors such as the time relationships between the drug use and the adverse reaction, response to drug withdrawal and re-administration, the presence or absence of other medications, and the patient medical history. Signal detection tools such as disproportionality analysis may also be useful in investigating the association between chemotherapy drug exposure and adverse reaction occurrence reported to the VigiBase**.**

5.4 Conclusion

The study aimed to analyze the global patterns of ADRs associated with the use of doxorubicin, epirubicin, and methotrexate using VigiBase data. The results showed that the top 10 reported ADR categories for each drug varied according to continents. However, blood and lymphatic, general and administration site, and gastrointestinal disorders were common across the continents for doxorubicin and epirubicin. In contrast, general and administration site conditions were the most prevailing reactions for methotrexate. Also, there were significant reports of injury, poisoning, and procedural complications from Africa and neoplasms from Asia.

Some significant associations were discovered suggesting potential high-risk demographic groups. Notably, Americas, Asia, and Europe were strongly associated with the likelihood of developing leukopenia. Also, males were more likely to develop neutropenic conditions, while children (ages 2-11 years) showed 3.33 times higher odds of developing pyrexia. Therapeutic or drug-ineffective issues were more likely to occur in males and elderly patients. Physicians should be aware of these patient groups in order to make informed decisions. Additional studies may also be required to characterize these findings further.

Certain ADRs identified in this study were not labeled in the approved PIs in South Africa. The main findings were off-label use, disease progression, constipation, decreased appetite, pulmonary embolism, pain, pneumonia, nervous system disorders, and drug therapy issues. Healthcare professionals and the SAHPRA should be aware of these potential risks.

In summary, this study has provided relevant insights into the pattern of reported ADRs for three specific oncology medicines commonly used globally and in South Africa. This study is a reminder for health professionals globally to be vigilant in monitoring and reporting adverse drug reactions in cancer chemotherapy. The findings from this study can also inform better clinical decision-making and proactive risk minimization in oncology healthcare settings and contribute to patient safety.

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APPENDICES

APPENDIX A: JOURNAL ARTICLE SUBMITTED FOR PUBLICATION

Title: Adverse Drug Reactions Associated with Doxorubicin and Epirubicin: a Descriptive Analysis from VigiBase

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Abstract

Background**:** Cancer is one of the leading causes of death globally. Owing to high toxicity, patients using chemotherapy drugs have a higher risk for developing adverse drug reactions (ADRs). Pharmacovigilance studies are essential in oncology to evaluate ADRs caused by anticancer drugs and improve patient safety. This study aimed to analyze serious ADRs associated with the use of doxorubicin and epirubicin reported to VigiBase.

Method: All anonymized data on suspected ADRs for doxorubicin and epirubicin as “serious” and "suspect” or "interacting” drugs between 1968 and 30th August 2021, was extracted from VigiBase. Descriptive statistics were conducted in Microsoft Excel and data was summarized using frequencies and percentages.

Results: A total of 35,620 serious individual case safety reports was analyzed. Majority of reports were from females (Dox= 61.41%; Epi= 86.56%) while the predominant age group was 45-64 years (Dox=42.06%; Epi=57.39%). Physicians were the more likely group to report serious ADRs (Dox=50.03%; Epi=34.11%). In general, Europe reported the highest for doxorubicin (38.08%) while Asia recorded the highest reports for epirubicin (53.28%). Oceania reported the least for both drugs (Dox=0.45%; Epi= 0.04%), followed by Africa (Dox=0.72%; Epi=0.29%). Blood and lymphatic system disorders was the most reported serious category [Dox= 11053 (44.47%); Epi=6659 (61.84%)]. The most common clinical manifestations were febrile neutropenia (Dox= 10.52%) and bone marrow failure (Epi= 23.89%).

Conclusion: This study provides relevant global insights into serious ADRs for doxorubicin and epirubicin. This knowledge may assist in minimizing and proactively managing ADRs. It can also inform policies to improve patient safety.

Keywords: Chemotherapy, epirubicin, doxorubicin, adverse drug reactions, VigiBase

1.0 Introduction

Cancer is a major global health burden and the second leading cause of death globally.[1] According to the World Health Organization (WHO),[1] about 19.3 million new cancer cases and 10 million deaths were estimated in 2020. Approximately 70% of these deaths are found to occur in low and middle-income countries.[1]

The increasing incidence and mortality have led to rapid developments in cancer therapies.[2] Of these, chemotherapy has been widely explored and hence mostly used.[3] However, its use is associated with a high incidence of adverse drug reactions (ADRs) owing to the intrinsic toxicity and narrow therapeutic index of the drugs.[4] A study conducted by Pearce et al.[5] showed that patients with cancer are vulnerable to ADRs with, 86% reporting at least one ADR during

chemotherapy. Globally, chemotherapy-related ADRs overburden healthcare systems, contributing to mortality, hospitalizations, increased therapy costs, and reduced quality of life.[6,7]

Anthracycline drugs are a backbone in cancer chemotherapy worldwide. They have proven efficacy as single agents or in combination chemotherapy in treating several types of solid tumours and haematological malignancies, with very few unresponsive cancers.[8] Among the anthracyclines available, doxorubicin and epirubicin have formed the mainstay of many chemotherapy regimens in clinical practice.[9,10] In South Africa, both drugs are routinely prescribed as an integral component of adjuvant therapy for surgically removed early breast cancer.[11] They act by inhibiting both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, thereby interfering with cancer cell replication and proliferation. This consequently affects host non-cancer cells leading to ADRs ranging from mild to fatal, if not managed promptly. The commonly reported ADRs are nausea, vomiting, mucositis, alopecia, myelosuppression.[12] Their use is also associated with severe but rare cardiotoxic risk, which often limits their long-term use.[13] A retrospective study reported cardiotoxicity following doxorubicin use as the most serious and potentially lethal ADR, with a 26% incidence, and 1-year mortality as high as 50%.[14] With the increasing use of these drugs, the risk of ADRs also increases. Hence, providing adequate drug monitoring is essential to enhance patient safety.

Pharmacovigilance (PV) is a major tool for monitoring the safety of drugs after market approval. According to the WHO,[15] pharmacovigilance is defined as "the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems". The popular Thalidomide tragedy characterized by the birth of babies with underdeveloped limbs in the late 1950s highlighted the urgent need for an international drug monitoring system and resulted in the birth of global pharmacovigilance.[16] During the clinical trials of a new drug, although a range of ADRs is identified, some ADRs only manifest after being used in larger populations.[17] Post-marketing surveillance is therefore a key aspect of pharmacovigilance that provides an avenue through which rare and population-specific ADRs can be detected.

The WHO, in 1968, established the Programme for International Drug Monitoring (PIDM), in collaboration with the Uppsala Monitoring Centre (UMC) located in Sweden.[18] The UMC collates individual case safety reports (ICSRs) through national PV centres in various countries to a pool of electronic ADR database known as VigiBase. VigiBase is the world's largest ADR repository with over 20 million reports submitted from 149 full member countries and it plays a major role in signal detection and patient safety studies.[18]

Spontaneous reporting is the most common approach to reporting in most countries and it constitutes the vast majority of reports submitted to the VigiBase.[19] It involves the voluntary reporting of ADRs by healthcare professionals or patients as they witness a reaction.[20] This reporting system may be limited by under-reporting of ADRs due to failure to recognize an ADR or inadequate knowledge of reporting procedures among healthcare professionals, resulting in incomplete data and undiscovered ADR signals.[21] Nonetheless, spontaneous reporting can

contribute substantially to early signal detection, especially for rare or serious reactions when efficiently deployed.[22]

Recently, given the huge scale of the COVID-19 vaccination programme amidst the pandemic, there have been concerted efforts towards spontaneous reporting for prompt detection of vaccine safety issues. While this is a notable stride, ADR monitoring is not only important for Covid 19 vaccine safety, but it should cut across all prevailing conditions and medicines used in their management. Unfortunately, PV is still lacking in many fields such as cancer chemotherapy. A previous study conducted by Baldo and colleagues highlighted under-reporting of chemotherapy-related ADRs to be a common phenomenon, especially in developing countries.[23]

In the field of oncology, where regimens are highly toxic and ADRs are often considered "normal" or often confused for underlying clinical symptoms, the role of PV cannot be overemphasized.[24] Investigating the safety profile of commonly used chemotherapy drugs in a global context would provide clinicians and policymakers with adequate knowledge needed to improve cancer patient safety.

1.1 Study Aim and Objectives

This study aimed to analyze serious suspected ADRs associated with the use of doxorubicin and epirubicin reported globally to VigiBase.

The specific objectives were:

i. To describe serious ADRs for doxorubicin and epirubicin according to demographic factors (gender, age group, and continent).

ii. To identify and quantify the top 30 reported serious ADRs for doxorubicin and epirubicin.

2.0 Methods

2.1 Study Design

A quantitative secondary analytical method was used to conduct this study. Data on ICSRs for doxorubicin and epirubicin in VigiBase was collated, analyzed, and interpreted.

2.2 Data Source

The data source utilized in this study was VigiBase, the WHO global database of ICSRs.[25] VigiBase contains ICSR data on conventional medicines, traditional medicines (herbals), biological products, and vaccines.

2.3 Data Extraction

The data set extracted from VigiBase contained all ICSRs for doxorubicin and epirubicin, registered by the reporter as "serious" and "suspect/interacting" drugs between 1968 and August 30th, 2020. Each ICSR recorded in VigiBase is an anonymized report for a single individual who experienced one or more adverse reactions that may be linked to the use of one or more drugs. All

ADRs in VigiBase have automatically been coded with the Drug Medical Dictionary for Regulatory Activities (MedDRA) terminology into a System Organ Class (SOC); which provides a broad definition of the system affected, and a Preferred Term (PT); which provides a precise identification of the reaction. All drugs recorded are coded according to WHODrug terminology.[25] The VigiBase data was electronically captured from the UMC into a Microsoft Excel spreadsheet, and each ICSR was extracted based on the following information:

i. Administrative information (report date, type of report, qualification of reporter or notifier)

ii. Patient data (unique report identification number, reporting continent, gender, age group)

iii. The drug involved (name, dose, indication for use, route of administration, drug status as suspect/interacting or concomitant drug, drug start and stop dates, dechallenge and rechallenge information, information on other concomitant drugs used).

iv. Characteristics of the reported ADR (MedDRA System Organ Class, Preferred Term, and Low-Level Term, time of onset of reaction, outcome of reaction, and seriousness criteria of ADR)

According to the WHO an ADR is characterized as "serious" if it resulted in death, is life-threatening, triggers hospitalization (or prolongation of existing hospitalization), causes a birth defect or congenital anomaly, leads to persistent incapacity or disability, or is judged clinically relevant by the physician who reports the case.[15]

2.4 Inclusion and Exclusion Criteria

All ICSRs for doxorubicin and epirubicin registered as "serious" and "suspect/interacting" were included in this study. Individual case safety reports with combination products (drugs containing suspect drugs in combination with other drugs), as well as patients with age group and gender unknown were excluded. Suspected duplicate ADRs were also excluded.

2.5 Data Analysis

Data was cleaned and sorted, and basic descriptive analysis was conducted using Microsoft Excel (Version 2016). ICSRs reported as "serious", "suspect/interacting" for doxorubicin and epirubicin were filtered and analyzed based on demographic factors (gender, age group, and continent). The top 30 serious ADRs were identified and quantified according to the MedDRA PTs using frequency tables, while the top 5 serious MedDRA SOCs were summarized using a frequency bar chart.

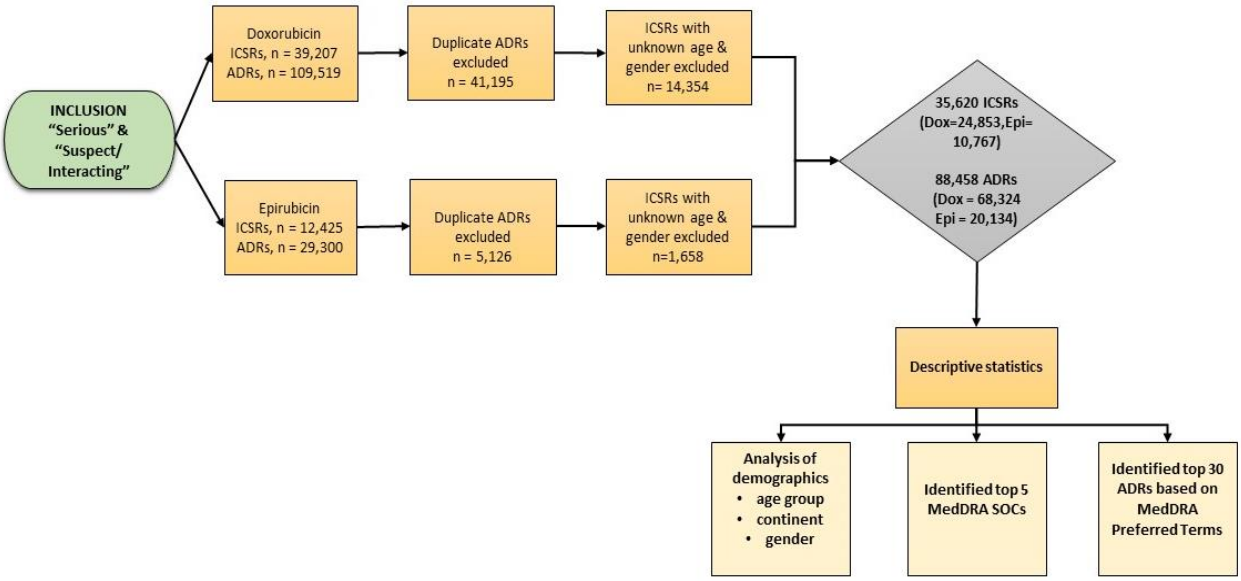

Figure 1: Study Flow Chart

3.0 Results

A total of 51,632 serious ICSRs (Dox= 39,207; Epi=12,425) and 138,819 ADRs (Dox=109,519; Epi=29,300) were retrieved from inception of WHO PIDM in 1968 to August 2020. Manual removal of 46,321 duplicates (i.e reports of the same ADR sent from multiple sources) resulted in a total of 92,498 ADRs (Dox=68,324; Epi=24,174). After excluding ICSRs with "unknown" age band and gender, 35,620 ICSRs (Dox= 24,853; Epi= 10,767), and 88,458 ADRs (Dox=68,324; Epi=20,134) were eligible for data analysis (Fig 1). The ADRs reported were found to be more than the ICSRs because more than one ADR can be reported for an individual patient.

3.1 Demographic Data

A total of 35,620 serious ICSRs was analyzed for both drugs. Majority of reports were from females (Dox= 61.41%; Epi= 86.56%) with the highest reports from Europe (Dox=39.75%) and Asia (Epi=62.96%).The predominant age group was 45-64years (Dox=42.06%; Epi=57.39%), with the majority of reports from Americas (Dox=37.28%) and Asia (Epi=56.24%). Physicians were the more likely group to report serious ADRs (Dox=50.03%; Epi=34.11%) with Europe recording the highest number of reports (Dox=48.87%; Epi= 82.79%). In general, Europe reported highest for doxorubicin (38.08%) while Asia recorded the highest reports for epirubicin (53.28%). Oceania reported the least for both drugs (Dox=0.45%; Epi= 0.04%), followed by Africa (Dox=0.72%; Epi=0.29%). Table 1 summarizes the demographic characteristics of serious ICSRs for doxorubicin and epirubicin.

Table 1: Demographic Characteristics of Serious Individual Case Safety Reports Associated with Doxorubicin and Epirubicin

Demographic characteristics	**Africa**		**Americas**		**Asia**		**Europe**		**Oceania**		**Total**	
	Dox	Epi	Dox	Epi	Dox	Epi	Dox	Epi	Dox	Epi	Dox	Epi
Gender, n (%)												
Female	116 (0.75)	24 (0.26)	5461 (35.78)	453 (4.86)	3552 (23.27)	4826 (51.78)	6068 (39.75)	4014 (43.07)	67 (0.43)	3 (0.03)	15264 (61.41)	9320 (86.56)
Male	63 (0.66)	7 (0.48)	3922 (40.90)	108 (7.46)	2163 (22.56)	911 (62.96)	3396 (35.41)	420 (29.02)	45 (0.47)	1 (0.07)	9589 (38.58)	1447 (13.44)
Age group, n (%)												
0-27 days	0 (0)	0 (0)	7 (21.21)	0 (0)	0 (0)	1 (5.56)	26 (78.79)	17 (94.44)	0 (0)	0 (0)	33 (0.13)	18 (0.17)
28 days to 23 months	1 (0.71)	1 (20)	68 (48.57)	2 (40)	28 (20)	1 (20)	41 (29.29)	1 (20)	2 (1.43)	0 (0)	140 (0.56)	5 (0.05)
2-11 years	12 (1.03)	0 (0)	551 (47.21)	4 (8.51)	244 (20.91)	23 (48.94)	357 (30.59)	20 (42.55)	3 (0.26)	0 (0)	1167 (4.70)	47 (0.44)
12-17 years	11 (1.09)	1 (2.44)	485 (47.97)	1 (2.44)	243 (24.03)	28 (68.29)	266 (26.31)	11 (26.83)	6 (0.59)	0 (0)	1011 (4.07)	41 (0.38)
18-44 years	57 (1.18)	14 (0.62)	1784 (36.79)	128 (5.64)	1242 (25.61)	1291 (56.87)	1751 (36.11)	836 (36.83)	15 (0.31)	1 (0.04)	4849 (19.51)	2270 (21.08)
45-64 years	80 (0.77)	10 (0.16)	3897 (37.28)	263 (4.26)	2568 (24.56)	3475 (56.24)	3862 (36.94)	2428 (39.29)	47 (0.45)	3 (0.05)	10454 (42.06)	6179 (57.39)
65-74 years	16 (0.31)	4 (0.22)	1831 (35.84)	121 (6.74)	958 (18.75)	721 (40.17)	2270 (44.44)	949 (52.87)	33 (0.65)	0 (0)	5108 (20.55)	1795 (16.67)
≥ 75 years	2 (0.10)	1 (0.02)	760 (36.35)	42 (10.19)	433 (20.70)	197 (47.82)	891 (42.61)	172 (41.75)	5 (0.24)	0 (0)	2091 (8.41)	412 (3.83)
Notifier, n (%)												

Physician	63 (0.50)	9 (0.24)	3847 (30.36)	169 (4.52)	2518 (19.87)	465 (12.42)	6192 (48.87)	3097 (82.79)	50 (0.39)	1 (0.03)	12670 (50.03)	3741 (34.11)
Pharmacist	74 (3.28)	13 (2.03)	512 (22.72)	28 (4.36)	596 (26.44)	145 (22.62)	1067 (47.34)	455 (70.98)	5 (0.22)	0 (0)	2254 (8.90)	641 (5.84)
Other Health Professional	38 (0.63)	8 (0.85)	3390 (56.35)	182 (19.38)	814 (13.53)	115 (12.25)	1737 (28.87)	633 (67.41)	37 (0.62)	1 (0.11)	6016 (23.76)	939 (8.56)
Lawyer	0 (0)	0 (0)	77 (71.96)	10 (18.51)	1 (0.93)	0 (0)	29 (27.10)	44 (81.48)	0 (0)	0 (0)	107 (0.42)	54 (0.49)
Consumer/ Non Health Professional	6 (0.32)	0 (0)	735 (39.39)	91 (19.91)	582 (31.19)	48 (10.50)	539 (28.89)	318 (69.58)	4 (0.21)	0 (0)	1866 (7.37)	457 (4.17)
Unspecified notifier	3 (0.12)	1 (0.02)	864 (35.83)	91 (1.77)	1396 (57.90)	4982 (97.04)	131 (5.43)	58 (1.13)	17 (0.71)	2 (0.04)	2411 (9.52)	5134 (46.82)
Total reports from each continent	179 (0.72)	31 (0.29)	9383 (37.75)	561 (5.21)	5716 (23.00)	5737 (53.28)	9464 (38.08)	4434 (41.18)	111 (0.45)	4 (0.04)	24853	10767

3.2 Frequency of Serious Adverse Drug Reactions According to System Organ Class Involved

The serious ADRs reported in this study involved all 27 MedDRA system organ classes. The top 5 serious system organ classes are displayed in Figure 2. The top 5 categories were consistent for both drugs, with blood and lymphatic system disorder being the most reported serious category [Dox= 11053 (44.47%); Epi=6659 (61.84%)].

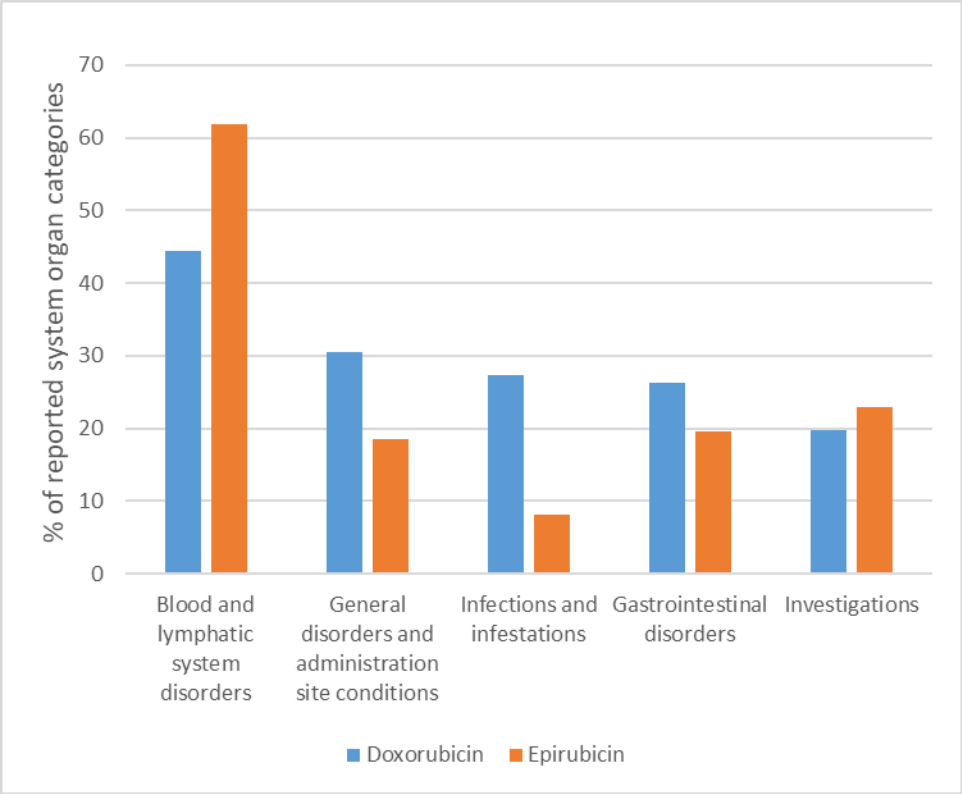

Fig 2: Top 5 Serious ADRs based on System Organ Class for Doxorubicin and Epirubicin

3.3 Frequency of Serious ADRs for Doxorubicin and Epirubicin based on MedDRA Preferred Terms

The frequency of the top 30 serious ADRs for both drugs is displayed in Table 2. The highest reported reaction for doxorubicin was febrile neutropenia (n=2615, 10.52%) followed by neutropenia (n=2370, 9.54%), while epirubicin had the highest report for bone marrow failure (n=2572, 23.89%).

Table 2: Top 30 Serious ADRs for Doxorubicin and Epirubicin in VigiBase

DOXORUBICIN (N=24853)		EPIRUBICIN (N=10767)	
Adverse Drug Reaction	**Frequency (%)**	**Adverse Drug Reaction**	**Frequency (%)**
Febrile neutropenia	2615 (10.52)	Bone marrow failure	2572 (23.89)
Neutropenia	2370 (9.54)	White blood cell count decreased	1433 (13.31)
Nausea and vomiting	2117 (8.52)	Nausea and vomiting	1118 (10.38)
Pyrexia	1532 (6.16)	Neutropenia	951 (8.83)
Anaemia	1069 (4.30)	Agranulocytosis	938 (8.71)
Off-label use/ product use in unapproved indication	1040 (4.18)	Febrile neutropenia	583 (5.41)
Bone marrow failure	1013 (4.08)	Pyrexia	569 (5.28)
Leukopenia	1001 (4.03)	Leukopenia	533 (4.95)
Thrombocytopenia	982 (3.95)	Thrombocytopenia	343 (3.19)
Dyspnoea	880 (3.54)	Neutrophil count decreased	317 (2.94)
Pneumonia	835 (3.36)	Diarrhoea	293 (2.72)
Diarrhoea	784 (3.15)	Anaemia	275 (2.55)
Pancytopenia	708 (2.85)	Alopecia	221 (2.05)
Sepsis	654 (2.63)	Hepatic function abnormal	190 (1.76)
White blood cell count decreased	559 (2.25)	Dyspnoea	177 (1.64)
Fatigue	528 (2.12)	Granulocytopenia	174 (1.62)
Mucosal inflammation	526 (2.12)	Asthenia	169 (1.57)
Asthenia	519 (2.09)	Cardiac failure	163 (1.51)
Abdominal pain	484 (1.95)	Acute myeloid leukaemia	145 (1.35)
Cardiac failure	466 (1.88)	Fatigue	135 (1.25)
Alopecia	458 (1.84)	Pancytopenia	129 (1.20)
Hypotension	445 (1.79)	Pneumonia	126 (1.17)
Malignant neoplasm progression	404 (1.63)	General physical health deterioration	105 (0.98)

Palmar-plantar erythrodysesthesia syndrome	400 (1.61)	Mucosal inflammation	95 (0.88)
Neutrophil count decreased	385 (1.55)	Cardiomyopathy	91 (0.85)
Disease progression	380 (1.53)	Pulmonary embolism	84 (0.78)
Platelet count decreased	379 (1.52)	Pain	76 (071)
Acute myeloid leukaemia	374 (1.50)	Ejection fraction decreased	74 (0.69)
Cardiomyopathy	367 (1.48)	Haemoglobin decreased	72 (0.67)
Acute kidney injury	366 (1.47)	Dehydration	70 (0.65)

4.0 Discussion

Chemotherapy is a mainstay of many clinical protocols for treating cancers locally and globally.[3] However, its clinical activity is limited due to the inherent toxicities of the drugs.[4] ADRs due to cancer chemotherapy are quite challenging as they negatively impact patients' quality of life and overburden healthcare systems.[26] This study, to our knowledge, is the first to analyze 'serious' ADRs associated with two commonly prescribed anthracycline chemotherapy drugs; doxorubicin and epirubicin, from a worldwide perspective. The results from this study provide some insights into reported serious ADRs for these drugs.

The majority of the ADRs (Dox= 61.41%, Epi= 86.56%) were reported in females, with the highest reports from Europe (Dox=39.75%) and Asia (Epi=62.96%). Globally, several study findings indicate that females are more prone to ADR than males[27]. A study done in 48 communities in the United Kingdom reported a total incidence of suspected ADRs in females as 20.6 per 10 000 patient months of exposure and 12.9 per 10 000 patient months of exposure in males.[28] Also, results from a survey involving ten prescription drugs withdrawn from the United States market indicated that eight of the drugs posed greater risks of adverse effects in women than men.[29] Another report from the Spanish Pharmacovigilance indicates that most suspected ADRs occur in women.[30] A review of 93 studies on ADRs associated with cardiovascular medications also reported 70% ADRs in females.[31] Our findings may be attributed to gender-wise variations that influence drug pharmacokinetics and subsequent toxicity.[32] For instance, due to differences in the expression levels of hepatic metabolic enzymes (CYP3A4), chemotherapy drugs tend to have a longer drug half-life and higher risk of toxicity in female patients than males.[33,34] Other essential factors include absorption, conjugation, renal elimination, and protein binding, which may also have gender-based differences.[27] Furthermore, studies indicate that females generally possess better healthcare-seeking attitudes compared to males, hence, they are more likely to report an ADR.[35]

The highest report of ADRs from this study was from Asia. This may be because Asia records almost half of the new cancer cases and more than 50% of the cancer mortality globally, indicating high consumption of cancer chemotherapy which may reflect more ADRs.[36] Also, the Pan-Asia have adapted the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the treatment of breast cancer which uses cyclophosphamide, doxorubicin and 5-FU (CAF) and cyclophosphamide, epirubicin and 5-FU (CEF).[37] This indicates high consumption of anthracyclines which may reflect the high ADRs reports of the drugs recorded in Asia and Europe.

The predominant age group was 45-64years (Dox=42.06%, Epi=57.39%), with the highest reports from the Americas (Dox=37.28%) and Asia (Epi=56.24%). Literature has shown that the prevalence of ADRs increases with age, which is consistent with our findings.[38] This may suggest a general decline in system organ capacity leading to low metabolizing capacity and reduced excretion. Consequently, this results in the accumulation of drugs in the body, increasing the risk of ADRs.[39] Hence, additional precautions should be taken while using chemotherapy in the elderly population. The highest ADRs recorded in the elderly were from Asia and America. Asia and North America have the highest elderly population globally, which probably may explain the results obtained.[40]

Physicians were the highest group of reporters (Dox=50.03%, Epi=34.11%) with the majority of the reports from Europe (Dox=48.87%; Epi= 82.79%). A recent study in the UK revealed that consumers generally reported more ADRs, however, healthcare professionals were found to report more serious ADRs that resulted in hospitalization or caused death.[41] Moreover, our findings may also be because only physician reporting was allowed for many years after establishing the first global ADR reporting systems in the 1960s.[42] Only a few countries like the United States and Sweden allowed non-physician reports, and patient/other healthcare professional reporting was only incorporated over time.[42] Till now, many countries have still not integrated consumer reporting into their national PV programme.

Europe recorded the highest reports (38.08%) for doxorubicin, whereas Asia recorded the highest reports (53.28%) for epirubicin (Table 1). Oceania reported the lowest for both drugs (Dox=0.45%, Epi=0.04%), followed by Africa (Dox=0.72%, Epi=0.29%). This finding may reflect the differences in drug utilization patterns and policies across various continents of the world. For instance, the low reports for epirubicin in the Americas (5.21%) may be due to its delayed approval by the Food and Drug Administration, compared to Europe, where it gained approval since 1980.[43] Also, previous studies have reported that epirubicin's use is favoured over doxorubicin in Asian countries, hence, the higher number of reports.[44] The low reports from Africa are in keeping with the literature, and it depicts the state of the health systems. PV systems in Africa are weak and lack resources and infrastructure compared to other developed countries.[21] In a global analysis conducted by Aagaard et al.[45], high-income countries generally reported high PV than low-income countries. While anti-neoplastic drugs constituted most of the reports from high-income countries, low-income countries such as Africa reported more ADRs for anti-infectives.[45] In line with past studies, our findings reflect a PV system in Africa that is not robust and only focuses on prevailing

conditions. Therefore, efforts should be made to provide resources and infrastructure to improve PV, particularly in the African setting.

Blood and lymphatic system disorders were the predominant system organ reported [Dox= 11053(44.47%); Epi=6659 (61.84%)] showing similar ADR manifestations for both drugs. Febrile neutropenia (Dox=10.52% of ICSRs) and bone marrow failure (Epi= 23.89% of ICSRs) were the most predominant reactions. This is in keeping with past literature as the risk of myelosuppression was found to be consistently higher in patients using anthracycline-based regimens.[46] While destroying cancer cells, anthracyclines are notorious for impairing rapidly dividing cells of bone marrow leading to a reduction of red blood cells, white blood cells, and platelets.[47,48] These manifestations are an important concern in clinical practice as they increase hospitalizations and the risk of infections owing to decreased immunity.[46] Therefore, this highlights the role of healthcare professionals in identifying patients at greatest risk and minimizing the risks since long-term therapy is essential for optimal treatment outcomes.

Nausea and vomiting constituted 8.52% and 10.38% of ICSRs for doxorubicin and epirubicin, respectively. Although typically considered non-lethal, previous studies have noted these symptoms to significantly impair quality of life, and result in non-adherence or even delayed treatment due to fear.[49,50] This is crucial as non-adherence and early discontinuation of chemotherapy have been identified as significant predictors of disease progression, and mortality in patients with cancer.[51] Hence, early interventions may be critical to prevent and proactively manage these reactions in patients.

The observed cardiotoxicities: cardiomyopathy (Dox= 1.88%, Epi= 0.85%), cardiac failure (Dox= 1.48%, Epi= 1.51%), and decreased ejection fraction (Epi= 0.69%) are in keeping with previous studies. This may be linked to the mechanism of oxidative stress and induction of cardiac muscle cell death.[52] Doxorubicin can cause myocardial damage in 1% to 20% of patients.[13] According to literature, epirubicin has a lower cardiotoxic risk than doxorubicin.[9] However, our findings could not particularly suggest if epirubicin is safer than doxorubicin since reports could have been influenced by variations in drug use and reporting biases. Baseline cardiac monitoring for patients undergoing treatment with both drugs is critical to ensure the benefits of drug use outweigh the risks. Likewise, children and adolescents should receive periodic cardiac evaluations since they have a high risk of delayed cardiotoxicity.

An interesting observation in this study is the “off-label use” of doxorubicin (n=1040, 4.18%). This suggests drug use in different populations, indications, or doses other than those for which it was licensed.[53] In the literature, the off-label use of doxorubicin includes management of multiple myeloma, advanced endometrial carcinoma, advanced renal cell carcinoma, and metastatic hepatocellular cancer.[54] Although its use may sometimes be clinically justified in oncology, a major drawback is a concern about patient safety, especially for drugs that have a high potential for toxicity like chemotherapy drugs. In a study conducted in Italy, off-label use significantly

increased the risk of serious ADRs in patients.[55] Further studies may be needed to assess off-label use of doxorubicin and regulatory actions should be taken where necessary.

Respiratory ADRs is another interesting and important set of findings from this study: pneumonia (Epi= 1.17%), pulmonary embolism (Epi= 0.78%), dyspnoea (Dox= 3.54%, Epi= 1.64%). Pneumonia has been reported to cause or complicate almost 10% of hospital admissions among cancer patients.[56-58] Past studies have suggested a link between epirubicin and pneumonia. For instance, Wijaya et al.[59] observed a high incidence of pneumocystis jirovecii pneumonia in metastatic breast cancer patients receiving weekly epirubicin-based regimens. Also, recently during a process of evaluating serious adverse event reports, the Korean Institute of Drug Safety (KIDS) found a causal association between epirubicin and pneumocystis jirovecii pneumonia which led to an update of the drug label (Pharmorubicin®).[60] Additional investigations may be required to identify patients at greatest risk who may benefit from antibiotic prophylaxis. While there is evidence for pneumonia associated with epirubicin in the literature, there is a dearth of data regarding pulmonary embolism and dyspnoea following anthracycline use and these could be potentially fatal signals requiring further assessment.

4.1 Study Limitations

The main strength of this global study is the use of VigiBase, covering many countries, involving diverse clinical settings and medical cultures over an extended period with a large sample of data. However, data from this study has some limitations. Firstly, the likelihood that the medicine caused the reported reactions varies from report to report. Hence, further causality studies may be needed.[61] Furthermore, data reported in VigiBase might be influenced by differences in health systems, drug utilization patterns, and policies over time and across various countries. Moreover, the data was retrieved according to continents, and it does not reflect which countries are making significant contributions. Hence, country-specific deductions could not be made. Lastly, the data from this study lacks complete clinical background information, such as existing patient co-morbidities which could hinder a complete interpretation of the ADRs.

5. 0 Conclusion

This study provides relevant global insights into serious reported ADRs for doxorubicin and epirubicin. It can assist healthcare professionals in early ADR identification and proactive risk management, which would improve patients' quality of life and treatment outcomes. It can also inform policies in improving cancer patient safety and serve as a platform for further pharmacovigilance studies.

Declaration of conflicting interests

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APPENDIX B: Sample of the VigiBase Data Extracted on Microsoft Excel Spreadsheet

	ReportID	FirstDateDatabase	ReportUpdatedDate	UN_Continent	WHO_Region	Serious	Seriousness	ReportType	Notifier	Age Group	Gender	WHODrugTradename
168	23424	20011116	20011116	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Male	Hydal
169	23424	20011116	20011116	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Male	Hydal
170	23424	20011116	20011116	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Male	Hydal
171	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Marcoumar
172	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Marcoumar
173	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Marcoumar
174	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Caelyx
175	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Caelyx
176	23535	20020130	20020130	Europe	European Region	-	-	Spontaneous	-	â‰¥ 75 years	Female	Caelyx
177	24240	20030224	20030224	Europe	European Region	-	-	Spontaneous	Physician	45 - 64 years	Female	Caelyx
178	24240	20030224	20030224	Europe	European Region	-	-	Spontaneous	Physician	45 - 64 years	Female	Caelyx
179	24240	20030224	20030224	Europe	European Region	-	-	Spontaneous	Physician	45 - 64 years	Female	Caelyx
180	24240	20030224	20030224	Europe	European Region	-	-	Spontaneous	Physician	45 - 64 years	Female	Caelyx
181	27844	19871231	19871231	Europe	European Region	-	-	Spontaneous	Physician	18 - 44 years	Male	Otrivine
182	27844	19871231	19871231	Europe	European Region	-	-	Spontaneous	Physician	18 - 44 years	Male	Adriblastina
183	32300	19990119	19990119	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Female	Taxol
184	32300	19990119	19990119	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Female	Taxol
185	32300	19990119	19990119	Europe	European Region	-	-	Spontaneous	-	45 - 64 years	Female	Doxorubicin

	WHODrugPreferredBaseName	WHODrugPreferredSaltName	Basis	Amount	AmountUnit	Frequency	FrequencyUnit	DrugTreatmentDuration	RouteOfAdministration	IndicationText
168	Hydromorphone	Hydromorphone hydrochloride	Concom	48.000000	Mg milligram(	-	-	-	-	-
169	Hydromorphone	Hydromorphone hydrochloride	Concom	48.000000	Mg milligram(	-	-	-	-	-
170	Hydromorphone	Hydromorphone hydrochloride	Concom	48.000000	Mg milligram(	-	-	-	-	-
171	Phenprocoumon	Phenprocoumon	Concom	-	-	-	-	-	Oral	-
172	Phenprocoumon	Phenprocoumon	Concom	-	-	-	-	-	Oral	-
173	Phenprocoumon	Phenprocoumon	Concom	-	-	-	-	-	Oral	-
174	Doxorubicin	Pegylated liposomal doxorubic	Suspect	80.000000	Mg milligram(	1.00000	Day	55.00000	Intravenous (not otherw	-
175	Doxorubicin	Pegylated liposomal doxorubic	Suspect	80.000000	Mg milligram(	1.00000	Day	55.00000	Intravenous (not otherw	-
176	Doxorubicin	Pegylated liposomal doxorubic	Suspect	80.000000	Mg milligram(	1.00000	Day	55.00000	Intravenous (not otherw	-
177	Doxorubicin	Pegylated liposomal doxorubic	Suspect	50.000000	Mg milligram(	-	-	-	Intravenous (not otherw	-
178	Doxorubicin	Pegylated liposomal doxorubic	Suspect	50.000000	Mg milligram(	-	-	-	Intravenous (not otherw	-
179	Doxorubicin	Pegylated liposomal doxorubic	Suspect	50.000000	Mg milligram(	-	-	-	Intravenous (not otherw	-
180	Doxorubicin	Pegylated liposomal doxorubic	Suspect	50.000000	Mg milligram(	-	-	-	Intravenous (not otherw	-
181	Xylometazoline	Xylometazoline hydrochloride	Concom	-	-	-	-	-	-	-
182	Doxorubicin	Doxorubicin hydrochloride	Suspect	1.000000	DF dosage for	1.00000	Month	54.00000	Intravesical	-
183	Paclitaxel	Paclitaxel	Suspect	290.00000	Mg milligram(	-	Total	0.00000	Intravenous (not otherw	Malignant neoplasm
184	Paclitaxel	Paclitaxel	Suspect	290.00000	Mg milligram(	-	Total	0.00000	Intravenous (not otherw	Malignant neoplasm
185	Doxorubicin	Doxorubicin	Suspect	100.00000	Mg milligram(	-	Total	0.00000	Intravenous (not otherw	Malignant neoplasm

	MeddraSOC_name	MeddraPT_name	MeddraLLT_nam	Outcome	ReactionDuration	DechallengeActio	DechallengeOutcom	RechallengeActio	RechallengeOutcom	TimeToOnset	Preferred_ReportId
167	Gastrointestinal disc	Melaena	Melaena	-	-	-	-	-	-	31.00000	0
168	Renal and urinary di	Renal impairment	Renal function abn	-	-	-	-	-	-	31.00000	0
169	Gastrointestinal disc	Diarrhoea	Diarrhoea	-	-	-	-	-	-	31.00000	0
170	Cardiac disorders	Cardiac failure	Cardiac failure	-	-	-	-	-	-	31.00000	0
171	Nervous system diso	Dysaesthesia	Dysaesthesia	Recovered/resolved	-	-	-	-	-	-	0
172	Gastrointestinal disc	Stomatitis	Stomatitis	Recovered/resolved	-	-	-	-	-	-	0
173	Skin and subcutaneo	Rash erythematous	Rash erythematous	Recovered/resolved	-	-	-	-	-	-	0
174	Nervous system diso	Dysaesthesia	Dysaesthesia	Recovered/resolved	-	Drug withdrawn	Reaction abated	Unknown	Effect unknown	61.00000	0
175	Gastrointestinal disc	Stomatitis	Stomatitis	Recovered/resolved	-	Drug withdrawn	Reaction abated	Unknown	Effect unknown	61.00000	0
176	Skin and subcutaneo	Rash erythematous	Rash erythematous	Recovered/resolved	-	Drug withdrawn	Reaction abated	Unknown	Effect unknown	61.00000	0
177	Vascular disorders	Flushing	Flushing	Recovered/resolved	-	-	-	-	-	-	0
178	Vascular disorders	Hypertension	Hypertension	Recovered/resolved	-	-	-	-	-	-	0
179	Skin and subcutaneo	Hyperhidrosis	Sweating increased	Recovered/resolved	-	-	-	-	-	-	0
180	Respiratory, thoracic	Dyspnoea	Dyspnoea	Recovered/resolved	-	-	-	-	-	-	0
181	Immune system diso	Hypersensitivity	Allergic reaction	Recovered/resolved	-	-	-	-	-	-	0
182	Immune system diso	Hypersensitivity	Allergic reaction	Recovered/resolved	-	Unknown	Not applicable	Unknown	Effect unknown	54.00000	0
183	Blood and lymphatic	Granulocytopenia	Granulocytopenia	-	-	Unknown	Not applicable	Unknown	Effect unknown	9.00000	0
184	General disorders ar	Pyrexia	Fever	-	-	Unknown	Not applicable	Unknown	Effect unknown	9.00000	0
185	Blood and lymphatic	Granulocytopenia	Granulocytopenia	-	-	Unknown	Not applicable	Unknown	Effect unknown	9.00000	0

APPENDIX C: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Miss Deborah Oloidi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M210866

NAME: (Principal Investigator)	Miss Deborah Oloidi
DEPARTMENT:	Pharmacy and Pharmacology
PROJECT TITLE:	Global patterns of adverse drug reactions related to doxorubicin, epirubicin, and methotrexate: analysis of individual case safety reports in vigibase
DATE CONSIDERED:	27/08/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr N. Padayachee
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/09/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

22/09/2021
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D: TURNITIN REPORT

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CHAPTER I

INTRODUCTION

1.1 Introduction

1.2 Background and Rationale

Final Dissertation

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