EVOLVING NATIONAL PHARMACOVIGILANCE SYSTEMS IN AFRICA

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CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

Pharmacovigilance is the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (1). Scientifically, pharmacovigilance relies on a wide range of basic and applied sciences for example, clinical pharmacology and biostatistics to determine the normal as well as the exaggerated effects of medical products including medicines and vaccines (2). Pharmacovigilance also involves implementing pharmacovigilance legislation, undertaking risk minimization activities and communicating safety issues to regulators, policy makers, health care professionals (HCPs) and the lay public. Pharmacovigilance therefore deals with a broad range of stakeholders, key of them being patients, HCPs, the national government and the pharmaceutical industry.

The World Health Organisation (WHO), the United Nations' specialised health agency, is responsible for coordinating global pharmacovigilance activities through the WHO Programme for International Drug Monitoring (PIDM) which is managed centrally by the safety and vigilance department at WHO, Geneva (3). The establishment of PIDM followed from tragic events in the 1960s, when several women who had taken thalidomide during pregnancy to prevent morning sickness gave birth to severely deformed children (3). Even though the birth defects caused by thalidomide were widespread, knowledge of their frequent worldwide occurrence was hampered by the lack of a global system for sharing information on the harm caused by medical products. As a result, the World Health Assembly launched a call for "a systematic collection of information on serious Adverse Drug Reactions (ADRs) during the development and, particularly, after medicines have been made available for public use", at its annual meeting in 1963 (4). This led to the establishment of the PIDM in 1968 (5).

The PIDM provides a governance structure to manage the conduct of pharmacovigilance activities by WHO member states and to collaborate on these activities across the globe. In order to participate in the PIDM, member states need to establish a national pharmacovigilance centre (national centre), a national spontaneous reporting system, a national database for collating ADRs, an advisory committee who advises on the safety of medicines and a communication strategy to help attain pharmacovigilance outcomes (5). Membership is then initiated through designation of an agency or institution as the national pharmacovigilance centre by a country's national government, which subsequently expresses in writing to the WHO a formal interest in becoming a PIDM member. Once this application is accepted, the Member State is referred to as an Associate Member of the PIDM. To become a Full Member, member states also need to demonstrate technical competence in passive surveillance and managing Individual Case Safety Reports (ICSRs) by submitting at least 20 ADRs of good quality to VigiBase®, which is the WHO global ICSRs database managed and maintained on behalf of the WHO by the Uppsala Monitoring Centre (UMC).

Whereas participation in the PIDM indicates existence of a formal and globally recognised national pharmacovigilance system, a wide range of other activities can be performed in pharmacovigilance systems to safeguard the public from medicine-related problems. These activities include early detection of hitherto unknown ADRs and interactions, identification of risk factors and possible mechanisms underlying ADRs, benefit-risk evaluation of medicines and dissemination of information needed to improve drug prescribing and regulation. In addition, pharmacovigilance also looks at the rational and safe use of medicinal products, product quality surveillance, genetic factors associated with medicines including pharmacogenetics and the economic impact of ADRs. To conduct these activities pharmacovigilance systems rely on the involvement of, and collaboration between, several different stakeholders along the entire healthcare, academic, industry and governmental value chain. In these systems, national pharmacovigilance centres are expected to coordinate, collaborate and liaise with all stakeholders involved.

Whilst many developed countries started to bring national pharmacovigilance activities under the umbrella of the PIDM early after its establishment in 1968, it took longer for most Low and Middle Income Countries (LMICs) to become part of the Programme and strengthen their national pharmacovigilance systems. The emergence and growth of national pharmacovigilance systems in LMICs have been plagued by challenges, key of them being fragmentation of activities, low ADR reporting to VigiBase®, limited knowledge and awareness of pharmacovigilance and lack of resources and expertise (6-10). This situation also applies to many African countries where pharmacovigilance systems often fulfill a limited number of functions and lack system capacity to protect the public from medicine-related harm. In African countries, pharmacovigilance has been considered for a long time as a public health activity that is conducted in universities or through professional doctors associations, rather than a regulatory activity backed by political legitimacy provided through laws, regulation and standards. However, with a relatively large number of African countries joining the PIDM and expanding national pharmacovigilance systems and associated activities this situation is gradually changing.

EMERGENCE OF PHARMACOVIGILANCE IN AFRICA

Africa was a relative late comer to pharmacovigilance (9). In the period between the start of the PIDM (1968) and the early 1980s, pharmacovigilance emerged in Africa through a series of mostly not well-documented and scattered meetings between stakeholders such as HCPs and national regulatory authorities which involved among others discussions about how to implement the PIDM governance structures. It was in the mid-1980s that some countries mostly the middle-income countries in Africa began passing national laws and became members of the PIDM. Morocco and South Africa were the first to join the PIDM in 1992, followed by Tanzania and Tunisia in 1993

and Zimbabwe in 1998. Ten other African countries joined the PIDM from 2000 to 2008, after which there was a sharp increase in membership, with eighteen countries joining the PIDM between 2010 and 2015. An overview of some key activities that took place during this period is provided in Table 1(5).

The early 2000s were marked with several continent-wide and global initiatives in pharmacovigilance. While pharmacovigilance was now considered an essential activity, the capacity to practice it was still limited. The WHO in Geneva, as well as the UMC in Sweden and the WHO collaborating centre for pharmacovigilance in Rabat, Morocco, undertook a focused approach to build pharmacovigilance capacity in Africa with the UMC alone training 100 African citizens since 1993 in its annual pharmacovigilance course (11). In 2002, the UMC and WHO also launched VigiBase® on-line (now called VigiFlow), an online ICSR management tool, particularly to enable countries without databases to submit ADRs and other drug safety data to the global ICSR database, VigiBase® (12). The United States Agency for International Development (USAID), working in particular with Management Sciences for Health (MSH), also supported pharmacovigilance activities in Africa during this period (13). However, the most direct impact on countries joining the PIDM comes from the establishment of an African hub to lead development of pharmacovigilance on the continent. In June 2009, the UMC established an African office (UMC– Africa) with dedicated funding, while the WHO designated the university of Ghana medical school (October 2009) as a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance (WHO–CC-Accra). Working hand-in-hand with UMC–Africa, the African hub (WHO–CC, UMC–Africa) undertook advocacy, country visits, in-country training and capacity building in several countries culminating in most of them becoming full members of the PIDM (Table 1). The rapid increase in African countries joining the PIDM since 2009 is due mainly to this focused continental effort (14), (15).

Beginning the year 2010, the international community recognised the drive for pharmacovigilance in Africa and as an advocacy effort held its two key meetings in pharmacovigilance in Africa: the PIDM annual national centres meeting and the International Society of Pharmacovigilance (ISoP) annual conference in Accra- Ghana in October/November 2010 (16). In this same period, African countries especially in Sub-Saharan Africa (SSA) shifted their focus from advocating for pharmacovigilance to lobbying national governments for the passing of pharmacovigilance laws and building organisations for conducting and coordinating pharmacovigilance activities. This effort is visible from the establishment of national pharmacovigilance centres in a number of countries. It also resulted in the passing of the first national pharmacovigilance policies in Nigeria and Eritrea (17), the only two countries in SSA with pharmacovigilance policies and the passing of the Qualified Person for Pharmacovigilance (QPPV) law in Ghana, currently the only country in SSA with a QPPV law (18). Further, this focused advocacy led to the establishment of organisations for pharmacovigilance such as

Table 1. Some key pharmacovigilance development activities in Africa (1990 - 2018)

Year	Activity	Activity Type
1992	Morocco, South Africa	PIDM Membership
1993	First Uppsala Monitoring Centre (UMC) pharmacovigilance training course involving African participants, Sweden	Trainings/Workshops
	Tanzania and Tunisia	PIDM Membership
2000	November 2000: 23rd annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring-PIDM (first in Africa)	Meetings/Initiatives
2001	October 2001: First annual meeting of the International Society of Pharmacovigilance (ISoP) held in Tunisia, Africa	Meetings/Initiatives
	Ghana	PIDM Membership
2002	Vigibase online for spontaneous data collection tool launched	Tool
2005	Mozambique, Nigeria	PIDM Membership
2007	July 2007: First WHO-African pharmacovigilance consultants network training for train the trainers in pharmacovigilance for Africa	Trainings/Workshops
	July 2007 : Formation of the Pharmacovigilance Sans Frontiers (PVSF): To lead pharmacovigilance advocacy and training across Africa	Organisations
2008	April 2008: Bill and Melinda Gates global strategy for pharmacovigilance meeting, Netherlands	Meetings/Initiatives
	Ethiopia, Sierra Leone	PIDM Membership
2009	June 2009 : Establishment of the Uppsala Monitoring Centre (UMC) -Africa office, Ghana	Organisations
	October 2009: Establishment of the WHO-CC for Advocacy & Training in pharmacovigilance, Ghana	Organisations
	December 2009: Launch of the USAID/MSH Indicator based Pharmacovigilance Assessment Tool (IPAT)	Tool
	Botswana, Madagascar, Namibia, Senegal, Sudan	PIDM Membership
	November 2010: Formation of the African Society of Pharmacovigilance (ASoP)	Organisations
	Burkina Faso, Cameroon, Cote d'Ivoire, Democratic Republic of Congo, Kenya	PIDM Membership
2011	November 2011: Establishment of the WHO collaborating centre for pharmacovigilance, Morocco	Organisations
	Benin, Mali	PIDM Membership
2012	Launch of the Pharmacovigilance Toolkit: An online resource for Pharmacovigilance	Tool
	March 2012: Launch of the East African Community (EAC) medicines registration harmonization project	Organisations
	October 2012: Launch of the Nigerian pharmacovigilance policy	Policy/Law
	Cape Verde, Eritrea, Niger	PIDM Membership

Table 1. (continued)

Year	Activity	Activity Type
2013	February 2013: Enactment of the Qualified Person for Pharmacovigilance (QPPV) law in Ghana	Policy/Law
	Angola, Guinea, Liberia, Rwanda	PIDM Membership
2014	May 2014: Declaration of Ghana FDA, Zimbabwe MCAZ, WHO-CC-Accra and others as Regional Centres of Regulatory Excellence (RCORE) in Pharmacovigilance by the African Union-African Medicines Harmonization (AMRH) initiative	Organisations
	September 2014: Launch of the Eritrean pharmacovigilance policy	Policy/Law
	Mauritius	PIDM Membership
2015	Launch of the WHO pharmacovigilance indicators	Tool
	Swaziland	PIDM Membership

the Pharmacovigilance Sans Frontiers (PVSF), the African Society of Pharmacovigilance (ASoP) and the African Union's, African Medicines Regulatory Harmonization (AMRH) initiative. The AMRH seeks to benchmark activities in pharmacovigilance across Africa by declaring some organisations as Regional Centres of Regulatory Excellence (RCORE) in pharmacovigilance (19). Currently, the AMRH initiative works through Regional Economic Communities (REC) to harmonise guidelines for regulation of medicines including pharmacovigilance activities leading to time reduction in the drug approval processes for marketing authorization holders. In addition, various reliance initiatives have been established. In the East African Community (EAC), regulatory authorities rely on each other for joint assessment of dossiers (20). In 2013, Zambia, Zimbabwe, Botswana and Namibia formed ZAZIBONA in the Southern Africa Development Community (SADC) region also for harmonization of the drug approval process in their countries (21). The Economic Community of West African States (ECOWAS) is yet to initiate any harmonization processes.

KEY CONTEXTUAL DRIVERS OF EVOLVING NATIONAL PHARMACOVIGILANCE SYSTEMS IN AFRICA

The past two decades have been a turning point for pharmacovigilance in Africa with involvement of African countries in the PIDM growing rapidly accompanied by the emergence and growing importance of regional organisations. All but one African country now have a national medicine regulatory agency (19). Currently (October 2018), thirty-six African countries are full members of the PIDM. Five countries (Algeria, Burundi, Gambia, Guinea Bissau and Malawi) are Associate Members working to attain the technical competence required for Full Membership while there are fourteen countries who are not members of the PIDM. The African Union (AU) and the WHO African Regional Office (WHO-AFRO) have fostered collaborations between African countries through various initiatives such as the East African Community harmonisation initiative aimed at countries sharing and leveraging their scarce resources to maximise outcomes including pharmacovigilance outcomes. Some of the drivers for this keen interest are:

Increased access to medicines: In the beginning of the 2000s, access to medicines in Africa for managing priority communicable diseases such as HIV/AIDS, malaria and tuberculosis became the key focus of most development partners due in part to the Millennium Development Goals (MDGs). Millennium Development Goal 6: Combat HIV/AIDS, malaria, and other diseases helped to mobilize funds for the treatment and care of patients including pharmacovigilance activities (22). Till date, donor organisations such as the Global Fund continually fund or procure medicines for priority diseases in all African countries including middle-income countries like Morocco and South Africa. With improved access came the need to monitor the safety of medications being administered. Some donor organisations such as the Global

Fund made the establishment or existence of adequate pharmacovigilance systems a requirement for supplying medicines to countries. As a result, countries had to develop pharmacovigilance systems that were acceptable to the Global Fund (23).

Changing disease burden: Due to improved socio-economic conditions in some countries in Africa, the disease burden of Africa has shifted to non-communicable diseases like cancer, stroke and other cardiovascular diseases, ischemic heart disease, diabetes, and dyslipidaemias in addition to the already high communicable disease burden. Non-communicable diseases will require long term medicine use, necessitating the need to monitor for their safety (24).

New medicines: Most new medicines tend to be licensed initially and used for years in the developed countries before being registered in developing countries. However, increasingly and especially in the area of infectious diseases some products are now specifically developed for and first used in Africa and other LMIC countries, such as the novel malaria vaccine, RTSS/AS01 (Mosquirix™), which was granted a positive scientific opinion by the European Medicines Agency in 2015. The WHO has however deferred policy recommendation for the widespread use of RTSS/AS01 (Mosquirix™), unless real-world studies are undertaken in Africa in relation to its safety, effectiveness and the programmatic issues surrounding its deployment. These studies are planned to take place in three African countries (Ghana, Kenya and Malawi) and are due to start in 2019 (25). This highlights the important role that national and regional pharmacovigilance systems will play in the development and use of medicines for conditions endemic in Africa.

WHY AND HOW TO STUDY EVOLVING NATIONAL PHARMACOVIGILANCE SYSTEMS IN AFRICA

A national pharmacovigilance system comprises of three key elements: people, functions and structures (26). In a comprehensive and well-functioning national pharmacovigilance system, these elements are interlinked and structures and people work in close concert with each other at various levels to fulfil a number of functions. The expected outcome of a functioning system is the prevention of medicine related-problems and ultimately reduced morbidity and mortality of patients (Figure 1). In most countries, the responsibility for overseeing and enforcing most of the legally-mandated core functions of the national pharmacovigilance system is shared between three structures: the national government (ministry of health), the national regulatory authority and the national pharmacovigilance centre. In most African countries the national pharmacovigilance centre is a department in the national regulatory authority. The first key function of the national pharmacovigilance system is ADR reporting which can be done spontaneously or through active surveillance approaches. Reporting by HCPs and patients can be done directly to national pharmacovigilance centres or indirectly to manufacturers who then have a legal

responsibility to report ADRs for their products as long as legislation is in place and enforced. Other institutions within the structure such as Public Health Programmes (PHPs) and academia are also expected to report on their pharmacovigilance related activities. The second key function of the national pharmacovigilance system is collation of the ADRs reported. The national pharmacovigilance centre is generally perceived as the organisation responsible for collating ADR reports and conducting initial analysis on them. Causality analysis, risk minimization and signal detection is a shared responsibility between three structures: the national pharmacovigilance centre, drug therapeutic committee and safety advisory committee. Evaluators, which typically are medical specialist, pharmacist or epidemiologists working at national pharmacovigilance centres or in the advisory and therapeutic committees, are responsible for conducting causality analysis and risk determination on the collated reports. The final key function of the national pharmacovigilance system is decision making and appropriate action based on the collated and analysed data. Regulatory actions may include package insert amendments, warnings, withdrawals and product recall. The regulatory authority is the structure responsible for regulatory actions for products on their markets. The dissemination of regulatory decision and actions are shared among several structures. The pharmaceutical industry is often held responsible for communicating on drug safety issues or decisions to HCPs. Health care professionals and professional groups can also distribute safety messages to various stakeholders. The PIDM distributes drug safety decisions to member states (26).

In the last decades, national pharmacovigilance systems in African countries have been gradually expanding the scope of their activities (Table 1). More than half of all African countries are PIDM members as of October 2018. They have national pharmacovigilance systems in place that reflect national priorities and work conducted in collaboration with the global community (5). These systems have been developed as part of efforts to eradicate priority diseases like HIV/AIDS, TB and malaria and they resemble the set-up of African healthcare delivery systems. In their further development there is a need to ensure that these systems are able to address the needs of the local population.

The fifty-four countries in Africa have unique healthcare delivery systems that differ from those in developed countries. The percentage of national budgets that is dedicated to healthcare is low and in almost all countries in Africa, a large proportion of healthcare delivery is through informal or non-governmental outlets and facilities (27). African countries rely heavily on donors and development partners for support in healthcare delivery resulting in a fragmented approach to treatment based on who the donor is and what conditions they are supporting. In addition, African countries do not have large research-based pharmaceutical industries and most medical products are imported (28). There is a relatively high circulation of substandard and counterfeit

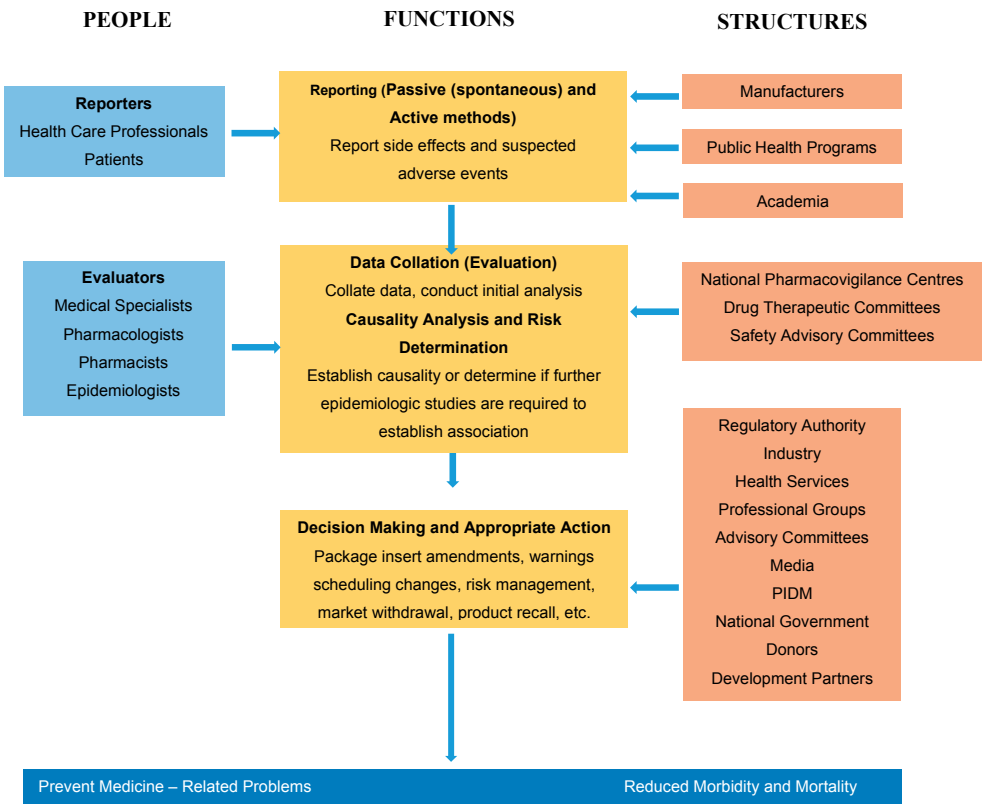

Figure 1. Elements of a national pharmacovigilance system (adapted from Strengthening Pharmaceutical Systems (SPS). Supporting Pharmacovigilance in Developing Countries: The Systems Perspective. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health). (26)

medicines (29) and medicine safety issues of public health concern are therefore not necessarily related to the rare, unknown ADRs of a product but also to the threat of harm associated with the use of substandard and counterfeit medicines. Further, African national governments do not prioritise pharmacovigilance systems as revealed by Stergachis et al in the review of 26 proposals from LMICs to the Global Fund (30). All these factors suggest that national pharmacovigilance systems will evolve along different paths from those taken by developed countries.

So far, there has been limited attention in academic studies to the expansion process and evolution of national pharmacovigilance systems in African countries. There is limited knowledge on how different types of pharmacovigilance functions are conducted in the various African countries, how different structures and people collaborate on various levels (local, national, international) when performing these functions and which types of scientific methods and evidence are fit-for-purpose and

fit-for-context to inform decisions on medication safety. There is also limited knowledge on the relationship between the establishment of national pharmacovigilance systems in African countries and the attainment of key pharmacovigilance outcomes such as assuring patient safety. By focusing on key structures, people and functions in the system, this thesis examines the evolution of national pharmacovigilance systems in African countries around three themes: 1) the role and position of national pharmacovigilance centres in the pharmacovigilance system, 2) the participation and awareness of reporters and evaluators in the generation of evidence and its use for policy decision making and 3) the feasibility of generating evidence on safety and use of medicines in clinical practice in the African setting.

THE ROLE AND POSITION OF NATIONAL PHARMACOVIGILANCE CENTRES

The national pharmacovigilance centre, typically a department under the regulatory authority is the structure responsible for coordinating pharmacovigilance at the national and international level within a country (31). At the national level, the national pharmacovigilance centre collaborates with other structures who engage in pharmacovigilance activities such as PHPs which are disease control programmes, academia, media, manufacturers and the pharmaceutical industry. At the country level, the national pharmacovigilance centre relies on all these institutions within the pharmacovigilance system to deliver its functions. At the international level, national pharmacovigilance centres collaborate with organisations like the PIDM typically through the submission of data to VigiBase®. The national pharmacovigilance centre has among its key functions, the collection of ADRs from reporters and processing these ADRs for evidence generation leading to decision making and appropriate actions as can be seen in (Figure 1). As the core functions of a pharmacovigilance system are conducted by the national pharmacovigilance centre, it is of key importance to evaluate its capacity to perform its functions.

Most African pharmacovigilance systems did not start from established national imperative or laws but rather in response to the need to deploy urgent interventions. Hence, most national pharmacovigilance systems were established ad hoc usually in connection with PHPs which are donor funded programmes. An example is the change in malaria policy from chloroquine to Artemisinin-Combination Therapy (ACT) which was the focus for the establishment of pharmacovigilance systems in several African countries such as Zambia, Eritrea, Kenya, Sierra Leone and Uganda among others (32). Once established, these nascent systems then has to be integrated into structures, such as the regulatory authority, by engaging policy makers to formulate laws to give legal backing to their activities. As a result, national pharmacovigilance centres were often not conceived as an integral part of the regulatory authority. In evolving national pharmacovigilance systems, these centres are defining their roles and positions within the system.

PARTICIPATION AND AWARENESS OF REPORTERS AND EVALUATORS

Currently, African reporting of ADRs is still limited and there seems to be room for improvement in the participation and awareness of reporters and evaluators in the pharmacovigilance system. Traditionally, market authorisation holders and HCPs are the main reporters of ADRs, however, patients can play a key role in reporting and several countries, especially in Europe and recently Ghana, are involving patients in the direct reporting of ADRs. Patient reports add new clinical information on ADRs which may lead to the strengthening of safety signals or identification of new ADRs (33), (34). Compared to HCPs, patients also report on different ADRs and drugs (35). For instance, a study in Portugal concluded that informing patients about ADR reporting and use of educational interventions could increase the number of ADR reports from patients (36). Patient reports have also been shown to contain a higher median number of suspected ADRs per report, and a more detailed description of reactions when compared to reports submitted by HCPs (37). So far in Africa, only Ghana is in the initial stages of implementing a patient reporting scheme (38). Other countries could learn from this initiative especially when it comes to stimulating patients and HCPs that participate in PHPs to report on ADRs.

Due to the high burden of neglected tropical diseases including onchocerciasis, schistosomiasis and soil-transmitted helminthiasis, mass drug administration (39) to patients is more frequent in Africa than in the developed world. Mass drug administration is associated with an increase in absolute numbers of ADR reporting since large populations of individuals are exposed which presents opportunities for ADR data collection. Not only is this type of data collection important for pharmacovigilance decision making but also for preventing, recognizing and managing ADRs which are the key patient management tasks for HCPs as far as medicines are concerned. When done correctly, it aids in improved therapy and protects patients from harm. In Africa, HCPs especially those in PHPs have an opportunity to collect data directly from patients because of the nature of these programmes which requires practitioners to actively follow up patients who have been administered medical products. It is therefore important to ascertain if any major policy decisions have been taken based on data collected from Africa.

GENERATING EVIDENCE ON SAFETY AND USE OF MEDICINES IN CLINICAL PRACTICE

One of the key functions of a pharmacovigilance system is collection of data on safety of medicines, which can be done in a passive (spontaneous) or active manner (Figure 1). Passive collection of pharmacovigilance data includes spontaneous reporting of ADRs that are submitted on a voluntary basis typically on a paper ADR form and eventually entered into a database for further assessment. The active manner of data

collection seeks to ascertain the complete number of adverse events via a continuous pre-organized process of following up with patients and products. The most commonly applied approaches to assess safety of medications is by collecting and using data from disease or product registries or electronic health records. Data can also be collected in clinical practice through prescription event monitoring, targeted spontaneous reporting and cohort event monitoring methods (40), (41). Active surveillance methodologies are usually applied to answer a specific safety question while spontaneous reporting can be used for generating safety signals that need further assessment, mostly via active surveillance methods.

In Africa, the two active surveillance methods promoted by the WHO are the targeted spontaneous reporting and cohort event monitoring (42). The targeted spontaneous reporting method is used to collate safety concerns suspected to be medicine related to a specific patient group who are on a particular medicine, example HIV patients. Targeted spontaneous reporting can be used not only to identify specific ADRs but also poor adherence to treatment due to adverse events. Cohort event monitoring aims to capture all medicine-related events such as problems due to safety, poor storage conditions, poor quality or counterfeit medicines, compliance and drug interactions in a defined group of patients during the course of routine practice. There is already some work done on both passive and active surveillance approaches in the African context. For instance Ankrah et al. (43) explored quantitative signal detection using databases for ADRs following immunizations in PHPs, Tetteh et al. (44) explored cohort event monitoring methodology to follow-up HCPs exposed to HIV for ADRs and adherence and Sagwa et al. (45) looked at a case/non-case disproportionality analysis using ADRs of patients treated for TB in VigiBase®.

The disparate nature of healthcare practices across Africa may however require different data collection approaches. African countries will continue to operate spontaneous reporting schemes regardless of the significant under-reporting associated with this method. However, although use of active surveillance methods is less well implemented or enforced in Africa these methods are and will be needed in the future to allow for a more comprehensive collection of safety data (9). It is estimated that by 2030, non-communicable diseases like cancers, diabetes and cardiovascular conditions will be responsible for the majority of deaths in Africa in addition to the existing burden of communicable diseases (46), (47). Several medical products will be used to manage these diseases. Several medicines currently being used in Africa were studied in clinical trials conducted elsewhere; it will be essential for Africa to have context specific methodologies for answering safety questions on real world use of these interventions. Active surveillance methodologies, especially cohort event monitoring studies, provide known denominators making it possible to calculate frequencies and where possible, identify factors associated with safety incidents (40). In order to ensure that the data collected from such studies are of high

quality, the data needs to be in line with tested and proven international standards such as International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Good Clinical Practices (GCP) requirements just as pertains in developed countries. The first steps in applying active surveillance methodologies to monitor safety in African patients have already been taken by others (43), (44), (45). However, the feasibility of applying active surveillance methodologies in low resource settings that are in line with international standards should be explored further.

STATEMENT OF RESEARCH AIM AND THESIS

Various authors have described the challenges associated with pharmacovigilance in Africa (7), (8), (9), (10). Despite such challenges the last decades have seen expansion and growth of African national pharmacovigilance systems most of them working with the PIDM. The aim of this thesis is therefore to provide insight into the emergence and growth of national pharmacovigilance systems in African countries by looking at different elements of the national pharmacovigilance system. Focus will be on examining the role and position of the national pharmacovigilance centre, the participation and awareness of reporters and evaluators and lastly, the feasibility of generating evidence on the safety and use of medicines in clinical practice in low resource settings in Africa.

THESIS OUTLINE

This thesis comprises six research studies organized into three chapters, followed by a general discussion about the implications of our findings, and recommendations for further academic research.

Chapter 2 examines the reporting function of the pharmacovigilance system from the perspective of the national centre. In Chapter 2.1, the VigiBase®, database of ADRs, is used to characterize ADR reporting activities in Africa and compare it with ADRs that are reported by the rest of the world. The national centre is also the focus of Chapter 2.2. The national centre is often considered to be responsible for coordinating pharmacovigilance at the national level, and in this chapter we examined how national centres in Africa utilize their resources and relationships to fulfil this mandate. Strategic leaders of eighteen national centres in Africa were interviewed to ascertain what they deemed successful and unsuccessful pharmacovigilance activities of their centres.

In order to increase reporting of ADRs to the national centre, the different stakeholders involved in pharmacovigilance need to be aware of their roles in the generation and use of pharmacovigilance data. Chapter 3 focuses on the people in the pharmacovigilance system and how they relate to functions focusing specifically on reporters (patients) and evaluators (HCPs). In Chapter 3.1 a mixed quantitative-

qualitative methodology is applied to understand the awareness of Ghanaian patients about ADRs and ADR reporting, whereas Chapter 3.2 explores through literature review, evidence based drug safety decision making in Africa by assessing if any major policy decisions have been taken based on data collected from Africa.

Chapter 4 assesses the feasibility of implementing different active pharmacovigilance methods to collect data on the safety of products in low resource settings in Africa. In Chapter 4.1 we assess if the active data collection methodology (modified cohort event monitoring) can be used to answer safety questions on first line therapies based on international guidelines, by assessing the safety profile of Injectable Artesunate in real world clinical setting. In addition, the feasibility of applying an active suveillance methodology in low resource settings with adherence to strict international research standards will be determined. Data collected through active surveillance methodologies was used to assess medicine prescription practices and to interrogate evidence on treatment, including sub-optimal dosing, of patients in clinical practice in low resource settings in Chapter 4.2. This was done by assessing if prescribers adhere to the WHO treatment guidelines on the use of injectable antimalarials for patients with severe malaria.

In Chapter 5, we present a general discussion of our results. We summarise the findings and discuss the challenges, opportunities and possible future approaches for effective pharmacovigilance in Africa.

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CHAPTER 2

THE ROLE AND POSITION OF NATIONAL PHARMACOVIGILANCE CENTRES

CHAPTER 2.1

ADVERSE DRUG REACTION REPORTING IN AFRICA AND A COMPARISON OF INDIVIDUAL CASE SAFETY REPORT CHARACTERISTICS BETWEEN AFRICA AND THE REST OF THE WORLD: ANALYSES OF SPONTANEOUS REPORTS IN VIGIBASE®

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ABSTRACT

Background

Following the start of the World Health Organisation (WHO) Programme for International Drug Monitoring (PIDM) by 10 member countries in 1968, it took another 24 years for the first two African countries to join in 1992, by which time the number of member countries in the PIDM had grown to 33. Whilst pharmacovigilance (PV), including the submission of individual case safety reports (ICSR) to VigiBase®, the WHO global ICSR database, is growing in Africa, no data have been published on the growth of ICSR reporting from Africa and how the features of ICSRs from Africa compare with the rest of the world (RoW).

Objectives

The objective of this paper was to provide an overview of the growth of national PV centres in Africa, the reporting of ICSRs by African countries, and the features of ICSRs from Africa, and to compare ICSRs from Africa with the RoW.

Methods

The search and analysis interface of VigiBase® VigiLyze® was used to characterise ICSRs submitted by African countries and the RoW. The distribution of ICSRs by African countries was listed and characterised by anatomic therapeutic chemical (ATC) code, Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) classification, and patient age and sex. The case-defining features of ICSRs between Africa and the RoW were also compared.

Results

The number of African countries in the PIDM increased from 2 in 1992 to 35 at the end of September 2015 and African PIDM members have cumulatively submitted 103,499 ICSRs (0.88 % of global ICSRs) to VigiBase®. The main class of products in African ICSRs are nucleoside and nucleotide reverse transcriptase inhibitors (14.04 %), non-nucleoside reverse transcriptase inhibitors (9.09 %), antivi- rals for the treatment of HIV infections (5.50 %), combinations of sulfonamides and trimethoprim (2.98 %) and angiotensin-converting enzyme (ACE) inhibitors (2.42 %). The main product classes implicated in ICSRs from the RoW are tumour necrosis factor-o (TNFo) inhibitors (5.29 %), topical nonsteroidal anti-inflammatory preparations (2.26 %), selective immunosuppressants (2.08 %), selective serotonin reuptake inhibitors (2.04 %) and HMG CoA reductase inhibitors (1.85 %). The main SOCs reported from Africa versus the RoW include skin and subcutaneous tissue disorders (31.14 % vs. 19.58 %), general disorders and administration site conditions (20.91 % vs. 30.49 %) and nervous system disorders (17.48 % vs. 19.13 %). The 18–44 years age group dominated ICSRs from Africa, while the 45–64 years age group dominated the RoW. Identical

proportions of females (57 % Africa and the RoW) and males (37% Africa and the RoW) were represented.

Conclusions

As at the end of September 2015, 35 of 54 African countries were Full Member countries of the PIDM. Although the number of ICSRs from Africa has increased substantially, ICSRs from Africa still make up 1 % of the global total in VigiBase®. The features of ICSRs from Africa differ to those from the RoW in relation to the classes of products as well as age group of patients affected. The gender of patients represented in these ICSRs are identical.

Key Points

As at the end of September 2015, 35 African countries were Full Members of the WHO Programme for International Drug Monitoring.

The 35 countries from Africa have submitted 103,499 (0.88 %) of the global total of 11,824,804 ICSRs in VigiBase® submitted by all 122 members of the PIDM.

ICSRs from Africa differ from the rest of the world in relation to the classes of products implicated and the age of patients.

INTRODUCTION

Pharmacovigilance (PV) is a relatively new science and public health activity in most African countries compared with industrialised countries. Before the year 2000, PV was not a priority in Africa due to several factors, including poor legislation for medicines regulation, lack of access to medicines and health commodities, weak and uncoordinated supply chains for medical products, lack of knowledge and awareness of PV, and lack of financial, human and technical resources for PV (1–3). Access to medicines in Africa for managing priority communicable diseases such as HIV/AIDS, malaria and tuberculosis has increased since 2000 due to concerted global efforts. In addition, the emerging middle class are able to pay out of pocket for their medical care, especially in relation to non-communicable diseases. The increased access to medicines and health commodities has shifted the national development agenda towards safe and cost effective use of these products and the establishment of surveillance systems for their safety, effectiveness and quality. National PV systems are therefore now beginning to emerge in Africa.

Globally, the existence of formal national PV systems is indicated by participation in the WHO Programme for International Drug Monitoring (PIDM). Membership of the PIDM is based on the existence of a designated national PV centre, a spontaneous adverse drug reaction (ADR) reporting system, and the demonstration of technical competence in managing individual case safety reports (ICSRs) by submitting at least 20 ICSRs to the global ICSR database, VigiBase®, maintained by the Uppsala Monitoring Centre (UMC), Sweden, on behalf of the World Health Organisation (WHO). The PIDM started with 10 members in 1968 following the thalidomide tragedy, and as of September 2015 had 122 Full Member countries, with 29 Associate Members awaiting full membership while compatibility between their national format and the international reporting formats is being established. ICSR reporting to VigiBase® is a useful indicator to measure and compare the national PV activity of countries, but it is important to highlight that PV is not just about spontaneous reporting and ICSR collection and submission; it involves several other surveillance, clinical and product quality assessment activities, including active PV and pharmacoepidemiological studies, medication error monitoring and the detection of products with compromised pharmaceutical integrity, including counterfeit and substandard medicines.

Although the PIDM started in 1968, the first African countries joined in 1992, and by 30 September 2015 a total of 35 of 54 African countries were Full Members of the PIDM. As yet, no comprehensive data have been published on PV, including ICSR reporting in Africa. A recent article by Isah et al. (3) provided a broad overview of the specific features and challenges of PV in Africa and identified the following constraints: weak human and material resources, poor training, irrational use of medicines, circulation of counterfeit medicines, high consumption of herbal medicines and weak pharmaceutical sector regulation. In terms of ICSR reporting in Africa, Berhe

et al. (4) recently examined the data in VigiBase® and noticed important differences in adverse drug reaction (ADR) reports for cardiometabolic drugs between Africa and the rest of the world (RoW). In particular, they noted differences in the age groups of patients, as well as higher reporting of ADRs to angiotensin-converting enzyme (ACE) inhibitors in African ICSRs compared with the RoW. The reasons behind such differences are important to ascertain as they may have implications for product and patient safety; however, the paucity of publications on PV in Africa makes this difficult. Researchers are therefore focusing on assessing the PV infrastructure in low- and middle-income countries (5) and how PV is being undertaken in important public health programmes such as malaria (6), HIV (7) and tuberculosis (8).

In view of the increasing number of African countries joining the PIDM and submitting data to VigiBase® (9), there is a need to understand the features of PV in Africa, including the main ICSR reporting countries, the number and types of ICSRs being submitted to the PIDM, the classes of products implicated in these ICSRs and the types of events reported. This work was therefore undertaken to provide information on the current PV situation in Africa, specifically ICSR reporting in Africa. Its main goal was to provide an overview of reporting activities in Africa and to compare the characteristics of ICSRs from Africa with those from the RoW. This will provide needed data to evaluate the progress of PV in Africa and give the WHO, national governments, the pharmaceutical industry and funding organisations a picture of PV in Africa.

OBJECTIVES

The objectives of this work were to characterise ICSR reporting activities in Africa and to compare them with the RoW by (i) documenting the development of PV in Africa in terms of countries joining the WHO PIDM; (ii) assessing the reporting of ICSRs to VigiBase® by national PV centres in Africa and identifying the top reporting countries; (iii) determining the main product classes, the main ADRs and the demographic features of African ICSRs and comparing these with the RoW.

METHODS

Data Source

The data source utilised in this quantitative study was VigiBase®, the global ICSR database (9). VigiBase® contains more than 11 million individual case reports of suspected ADRs submitted since 1968 by the 122 member countries of the WHO Programme. It represents the official and most authoritative data source for ICSR reporting globally. VigiBase® contains ICSR data on conventional medicines and traditional medicines (herbals), as well as biological products and vaccines.

Data Analysis

Quantitative data analysis was undertaken on the number of ICSRs submitted by each African country, as well as the types of products and ADRs in these ICSRs. These data were extracted from VigiBase®. Similar analysis was also undertaken for the RoW. ICSRs from Swaziland, who became members in 2015, are not included in the cumulative counts since they were entered closer to the data analysis cutoff date (30 September 2015) and are yet to be incorporated into the analysis section of VigiBase®. The analysis was performed by using the search and analysis interface of VigiBase®, known as VigiLyze®, and Microsoft SQL queries. Using the query interface with predefined filters, data were pulled on reporting statistics, substances or products and ICSRs in a line listing report output. These queries were then saved and the output exported to Microsoft Excel™ (Microsoft Corporation, Redmond, WA, USA). The year of joining the WHO Programme as Full Members by individual countries was obtained from the website of the WHO PIDM, the UMC (http://www.who-umc.org), and the population of each country per year was obtained from the United Nations (http://www.unfpa.org/swop). The population for each year was summed from the year they joined the programme, in order to obtain the cumulative population, which was then used for the calculations below.

The ICSR data were normalised to take into account the length of time a country has been in the PIDM, as well as the population size, by expressing the ICSRs as number of reports per million person-years. In order to know the main product classes implicated in ICSRs, all products reported as suspected of causing a reaction were aggregated on the fourth-level ATC code, and the number of times a product class was reported was counted. Combination products, by definition, ended up being counted in terms of their individual components so the number of individual active substances and ATC codes may be more than the number of products. Since a few active ingredients have more than one ATC code, the total number of product classes expressed may be slightly higher than the actual number of classes in the submitted ICSRs but this is unavoidable. The ADRs in the ICSRs were identified by aggregating coded ADRs in each ICSR using the Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) classification. The age and gender of patients in each ICSR were extracted and aggregated for both Africa and the RoW.

RESULTS

Growth of national pharmacovigilance (PV) centres and reporting of ICSRs in Africa

The 35 African countries who are Full Members of the PIDM, their year of joining and the number of reports (ICSRs) they have submitted since joining the PIDM are shown in Table 1. Morocco and South Africa were the first to join in 1992, followed by Tanzania and Tunisia in 1993 and Zimbabwe in 1998. Ten other African countries

joined the PIDM from 2000 to 2008, after which there was a sharp increase in membership, with 18 countries joining the PIDM in the 5-year period from 2010 to 2015.

Reporting of ICSRs from Africa is extremely low compared with the RoW, with the cumulative number of ICSRs from Africa to VigiBase standing at 103,499 ICSRs, which is equivalent to 0.88 % of the global total number of 11,824,804 ICSRs in VigiBase at 30 September 2015. The main ICSR reporting countries in Africa in terms of cumulative data in VigiBase include South Africa, Morocco, Nigeria, Egypt and Kenya (Table 2). South Africa, Morocco and Nigeria alone account for more than half of the African ICSRs in VigiBase. When the ICSRs are expressed per million person-years (Table 1), which normalises ICSRs to take into account population size as well as

Table 1. Full members of the Programme for International Drug Monitoring in Africa

Country	Year of joining	No. of ICSRs to 2015	No of ICSRs per million person years
Angola	2013	239	5.48
Benin	2011	29	0.71
Botswana	2009	103	8.60
Burkina Faso	2010	76	0.92
Cameroon	2010	46	0.42
Cape Verde	2012	247	165.67
Congo, the Democratic Republic of	2010	5558	16.90
Côte d'Ivoire	2010	28	0.28
Egypt	2002	8474	8.62
Eritrea	2012	1982	104.31
Ethiopia	2008	803	1.28
Ghana	2001	2900	9.07
Guinea	2013	31	1.30
Kenya	2010	8440	39.07
Liberia	2013	42	4.83
Madagascar	2009	1087	8.23
Mali	2011	80	1.33
Mauritius	2014	39	31.22
Morocco	1992	17,231	25.38
Mozambique	2005	797	3.36
Namibia	2009	1604	119.25
Niger	2012	39	0.72
Nigeria	2005	10,590	6.70
Rwanda	2013	29	1.21
Senegal	2009	181	2.44
Sierra Leone	2008	1272	30.97
South Africa	1992	28,609	27.22
Sudan	2009	38	0.20

Table 1. (continued)

Swaziland	2015	27	19.02
Tanzania, United Republic of	1993	1360	1.68
Togo	2008	311	6.86
Tunisia	1993	6990	32.14
Uganda	2008	1871	7.59
Zambia	2010	218	3.09
Zimbabwe	1998	2155	9.77

ICSRs individual case safety reports
[a] Data from VigiBase® to 30 September 2015. Cumulative population to 2014 was used as 2015 data were not yet available

Table 2. Main African reporting countries

Country	No. of ICSRs in VigiBase®	Percentage of total African ICSRs[a] in VigiBase®
South Africa	28,609	27.64
Morocco	17,231	16.65
Nigeria	10,590	10.23
Egypt	8474	8.19
Kenya	8440	8.15
Tunisia	6990	6.75
Congo, the Democratic Republic of	5558	5.37
Ghana	2900	2.80
Zimbabwe	2155	2.08
Eritrea	1982	1.91

ICSRs individual case safety reports
[a] Total ICSRs from all African countries to 30 September 2015 (excluding Swaziland, n = 27) was 103,499

the length of time a country has been in the PIDM, the top countries included Cape Verde, Namibia, Eritrea, Kenya, Tunisia, South Africa and Morocco.

Product Classes Implicated in Individual Case Safety Reports (ICSRs) from Africa and the Rest of the World (RoW)

The main product classes implicated in ICSRs from Africa are shown in Table 3, which is dominated by classes of products for treating HIV/AIDS, namely nucleoside and nucleotide reverse transcriptase inhibitors (14.04 %), non- nucleoside reverse transcriptase inhibitors (9.09 %), and antivirals for treatment of HIV infections (5.50 %).

Others include combinations of sulfonamides and trimethoprim, including derivatives (2.98%), ACE inhibitors, plain (2.42 %), antibiotics (2.26 %), meningococcal vaccines (2.23 %), interferons (2.06 %) and combination products for tuberculosis (1.87 %). In contrast to African ICSRs, there is no single dominant product class in RoW

reports (Table 4). The classes of products commonly reported in ICSRs from the RoW (Table 4) include tumour necrosis factor-a (TNFa) inhibitors (5.29 %), anti-inflammatory preparations, nonsteroids for topical use (2.26 %), selective immunosuppressants (2.08 %), selective serotonin reuptake inhibitors (2.04 %), and HMG CoA reductase inhibitors (1.85 %).

Adverse drug reactions in ICSRs from Africa and the RoW

In SOC classification, African ICSRs are dominated by reports of skin and subcutaneous tissue disorders (31.14 %), general disorders and administration site conditions

Table 3. Top 10 product classes in African reports vs. RoW reports

ATC code	Africa (%)[a]	RoW (%)[b]
J05AF—nucleoside and nucleotide reverse transcriptase inhibitors	14,530 (14.04)	44,055 (0.38)
J05AG—non-nucleoside reverse transcriptase inhibitors	9407 (9.09)	26,107 (0.22)
J05AR—antivirals for the treatment of HIV infections, combinations	5692 (5.50)	34,927 (0.30)
J01EE—combinations of sulfonamides and trimethoprim, incl. derivatives	3082 (2.98)	81,206 (0.69)
C09AA—ACE inhibitors, plain	2503 (2.42)	154,176 (1.32)
S01AA—antibiotics	2340 (2.26)	179,635 (1.53)
J07AH—meningococcal vaccines	2308 (2.23)	48,480 (0.41)
L03AB—interferons	2130 (2.06)	211,098 (1.80)
J04AM—combinations of drugs for treatment of tuberculosis	1933 (1.87)	7043 (0.06)
D06AX—other antibiotics for topical use	1855 (1.79)	103,228 (0.88)

RoW rest of the world, ATC anatomic therapeutic chemical, ACE angiotensin-converting enzyme, ICSRs individual case safety reports
[a] Percentage includes all African ICSRs (n = 103,499) in VigiBase® (excluding Swaziland, n = 27)
[b] Percentage of all RoW ICSRs (n = 11,721,305) in VigiBase®

Table 4. Top 10 product classes in RoW reports vs. African reports

ATC code	RoW (%)[a]	Africa (%)[b]
L04AB—tumour necrosis factor alpha inhibitors	619,737 (5.29)	939 (0.91)
M02AA—antiinflammatory preparations, non-steroids for topical use	265,138 (2.26)	1350 (1.30)
L04AA—selective immunosuppressants	243,382 (2.08)	238 (0.23)
N06AB—selective serotonin reuptake inhibitors	238,611 (2.04)	718 (0.69)
C10AA—HMG CoA reductase inhibitors	217,302 (1.85)	936 (0.9)
M01AE—propionic acid derivatives	214,595 (1.83)	738 (0.71)
L03AB—interferons	211,098 (1.80)	2130 (2.06)
N05AH—diazepines, oxazepines, thiazepines and oxepines	205,773 (1.76)	650 (0.63)
N06AX—other antidepressants	201,461 (1.72)	1398 (1.35)
N03AX—other antiepileptics	187,813 (1.60)	959 (0.93)

RoW rest of the world, ATC anatomic therapeutic chemical, ICSRs individual case safety reports
[a] Percentage of all RoW ICSRs (n = 11,721,305) in VigiBase®
[b] Percentage of all African ICSRs (n = 103,499) in VigiBase® (excluding Swaziland, n = 27)

(20.91 %), nervous system disorders (17.48 %) and gastrointestinal disorders (16.10 %), as shown in Table 5. These are followed by respiratory, thoracic and mediastinal disorders (5.71 %), investigations (5.07 %), blood and lymphatic system disorders (5.04 %), psychiatric disorders (4.72 %), musculoskeletal and connective tissue disorders (4.36 %) and infections and infestations (3.78 %). The main ADRs in the RoW reports (Table 6) are not dissimilar from those reported in Africa and include general disorders and administration site conditions (30.49 %), skin and connective tissue disorders (19.58 %), nervous system disorders (19.13 %), and gastrointestinal disorders (17.86 %).

Table 5. Top 10 SOCs in African reports vs. RoW reports

SOC	Africa (%)[a]	RoW (%)[b]
Skin and subcutaneous tissue disorders	32,225 (31.14)	2,295,539 (19.58)
General disorders and administration site conditions	21,642 (20.91)	3,574,082 (30.49)
Nervous system disorders	18,094 (17.48)	2,242,378 (19.13)
Gastrointestinal disorders	16,662 (16.10)	2,093,534 (17.86)
Respiratory, thoracic and mediastinal disorders	5912 (5.71)	1,046,599 (8.93)
Investigations	5245 (5.07)	1,080,507 (9.22)
Blood and lymphatic system disorders	5219 (5.04)	523,173 (4.46)
Psychiatric disorders	4890 (4.72)	1,042,390 (8.89)
Musculoskeletal and connective tissue disorders	4512 (4.36)	905,026 (7.72)
Infections and infestations	3912 (3.78)	846,842 (7.22)

SOC system organ class, RoW rest of the world, ICSRs individual case safety reports
[a] Percentage of all African ICSRs (n = 103,476) in VigiBase® (excluding Swaziland, n = 27)
[b] Percentage of all RoW ICSRs (n = 11,721,305) in VigiBase®

Table 6. Top 10 SOCs in RoW reports vs. African reports

SOC	RoW (%)[a]	Africa (%)[b]
General disorders and administration site conditions	3,574,082 (30.49)	21,631 (20.91)
Skin and subcutaneous tissue disorders	2,295,539 (19.58)	32,225 (31.14)
Nervous system disorders	2,242,378 (19.13)	18,094 (17.48)
Gastrointestinal disorders	2,093,534 (17.86)	16,662 (16.10)
Investigations	1,080,507 (9.22)	5245 (5.07)
Respiratory, thoracic and mediastinal disorders	1,046,599 (8.93)	5912 (5.71)
Psychiatric disorders	1,042,390 (8.89)	4890 (4.72)
Injury, poisoning and procedural complications	946,308 (8.07)	3008 (2.91)
Musculoskeletal and connective tissue disorders	905,026 (7.72)	4512 (4.36)
Infections and infestations	846,842 (7.22)	3912 (3.78)

SOC system organ class, RoW rest of the world, ICSRs individual case safety reports
[a] Percentage of all African ICSRs (n = 11.721,305) in VigiBase®
[b] Percentage of all RoW ICSRs (n = 103,499) in VigiBase® (excluding Swaziland, n = 27)

Patient Characteristics: Africa vs. the RoW

The dominant age group from Africa was 18–44 years (39.10 %) compared with the RoW, which is dominated by an older age group of 45–64 years (24.13 %) (Figure 1). A significant proportion of reports from both Africa (16.18 %) and the RoW (26.00 %) failed to mention the age group of those affected, highlighting the incompleteness of a good number of ICSRs submitted to VigiBase®. The gender of patients in African and RoW ICSRs are identical for females (57 % Africa vs. 57 % RoW) and males (37 % Africa vs. 37 % RoW). Six percent of reports from both Africa and the RoW did not specify the gender.

DISCUSSION

Growth of PV in Africa and features of ICSR reporting to VigiBase®

Africa was a late comer to global PV, with the first countries becoming involved 24 years after the PIDM started. Whilst the 24-year gap raises troubling questions as to the types of vaccine and medicine safety incidents that may have gone unrecorded, the fact remains that in 2015 there are still 21 African countries who are not members of the PIDM. The growth of African PV in terms of countries joining the PIDM started more as a trickle than a concerted continental effort. From 1992 to 2000, there were

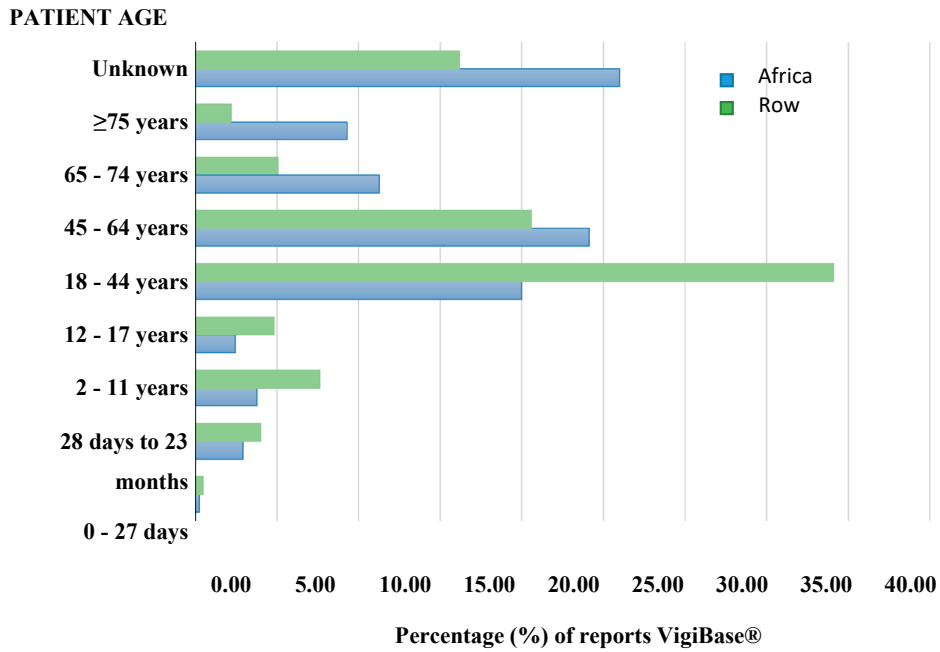

Figure 1. Age graphs for Africa and the Rest of the World from 1992 to 30 September 2015

only five African members of the PIDM before membership gathered pace in the new millennium. Why did it take so long for African countries to start joining the PIDM and what were the factors underlying this movement? The factors are many and diverse and some authors have mentioned important health system obstacles to PV growth in Africa, including weak overall national health infrastructure and systems, poor understanding of PV, lack of PV in the formal curriculum and low interest by healthcare professionals (10-14).

The steady growth in PIDM membership from 2000 could be due to several factors. The Millennium Development Goals and its focus on health improvement, as well as prevention of infant and maternal mortality, firmly shifted the development agenda to healthcare delivery and health system strengthening in poor countries. The establishment of the Global Fund against HIV/AIDS, Tuberculosis and Malaria (Global Fund), as well as other important global health initiatives (US President's Emergency Plan for Aids Relief [PEPFAR], US President's Malaria Initiative, the Bill and Melinda Gates Foundation, etc.) brought in huge financial resources that enhanced access to medicines (15). With increased access to medicines, the need to monitor their safety became obvious. The Global Fund, for instance, insisted on safety monitoring of all its products as a key requirement for grant recipients as early as 2002, although research indicates that this was only partially adhered to (16), with improved adherence occurring only after the Fund included a mandatory field relating to PV on all grant application forms in 2010. The WHO in Geneva, as well as the UMC in Sweden and the WHO Collaborating Centre for PV in Rabat, Morocco, undertook a focused approach on PV capacity building in Africa, with the UMC alone training 100 Africans since 1993 in its annual PV course. The United States Agency for International Development (USAID), working in particular with Management Sciences for Health (MSH), also supported PV activities in Africa. However, the most direct impact on countries joining the PIDM comes from the establishment of an African hub to lead PV development on the continent. In June 2009, the UMC established an African office (UMC– Africa) with dedicated funding, while the WHO designated the University of Ghana (October 2009) as a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance (WHO–CC), working hand-in-hand with UMC–Africa. The African hub (WHO–CC, UMC–Africa) undertook advocacy, country visits, in-country training and capacity building in several countries, culminating in most of them becoming full members of the PIDM. The rapid increase in African countries joining the PIDM since 2009 is due mainly to this focused continental effort.

In relation to ICSR reporting to VigiBase®, the data suggest that nearly one-third of the countries in Africa submit enough data (at least 20 ICSRs) to gain membership of the PIDM, after which there is a pause. Currently 10 countries have submitted less than 100 ICSRs to VigiBase®. Poor reporting of ICSRs hinders signal generation. However, for sustainable PV systems, reporting and signal generation needs to be

embedded in wider health system-related policies and infrastructures, and this is currently not the case in many countries. For instance, a 2009 survey of PV in 46 sub-Saharan African countries (17) showed that less than half have a national policy that covers PV and 72 % do not have a legal mandate to monitor medicine-related adverse events. Furthermore, only 39 % have national PV guidelines or a national safety advisory committee, and only 28 % have a platform or strategy to coordinate PV at the national level. While African membership of the PIDM has increased, the poor reporting of ICSRs is an indication that health system issues have not been adequately dealt with.

Another survey might be necessary to identify appropriate interventions for improving ICSR reporting in Africa. Africa's population of over 1 billion (15 % of the global total) and its healthcare features (high number of infectious diseases, e.g. HIV/ AIDS, tuberculosis, malaria, etc., and increasing incidence of noncommunicable diseases) means that the population is exposed to a high number of medical products, which should theoretically translate to high ICSR reporting. The low number of ICSRs (1 % of ICSRs in VigiBase®) is an indication of weak PV activity, especially when one considers the fact that several of the priority diseases in Africa are managed through formal, reasonably well-funded public health programmes that administer large numbers of medicines to millions of individuals annually. The relatively high ICSR reporting countries in Africa appear to be those with an active pharmaceutical industry presence or strong public health programmes.

Classes of products implicated in ICSRs from Africa

The main product classes implicated in ICSRs are anti- infectives, notably antiretrovirals and antibiotics. The domination of HIV/AIDS products in African ICSRs is perhaps not surprising considering the high burden of HIV/AIDS on the continent. With well-funded programmes providing access to antiretrovirals, it is expected that there would be more ICSRs on these products since healthcare workers in these programmes tend to be trained in PV. Indeed, most published PV studies from Africa tend to be on the safety of antiretrovirals (18, 19). The relatively high number of reports to ACE inhibitors may be an indication of the changing morbidity patterns on the continent with a steeply increasing burden of communicable diseases, in addition to the persisting dominance of noncommunicable diseases as noted and reported by the WHO, the UN and several other players (20–22). It is interesting to note that the article by Berhe et al. (4), which examined ADRs to cardiometabolic drugs, found a disproportionately higher reporting of ADRs to ACE inhibitors when comparing ICSRs from sub-Saharan Africa with the RoW (36 % vs. 14 %). Differences such as these underscore the importance of improving ICSR reporting from Africa in order to improve the chances of detecting any African-specific safety issues. The presence of the meningococcal vaccine among the top product classes implicated in African ICSRs

may be due to the recent large-scale roll out of the meningococcal vaccine across West Africa in response to outbreaks. This particular programme was accompanied by a concerted PV effort. The vaccines that are widely used in national childhood immunisation programmes in Africa did not feature among the main product categories reported, a strong suggestion that systems for monitoring adverse events following immunization may be absent or that national expanded programmes on immunization do not submit safety data to national PV centres and to VigiBase®.

Main ADRs in African ICSRs

The main SOC reported in African ICSRs relate to the expected ADRs of the product classes in African ICSRs. General disorders, skin and appendage disorders and nervous system disorders are among the most frequent and easily identifiable event types reported to antiretrovirals and antibiotics. The presence of 'investigations' among the ADRs in African ICSRs could be due to the public health programmes which provide routine laboratory investigations as part of standard care since laboratory investigations are rarely carried out in routine care in Africa due to cost considerations. Representing the ADRs reported as SOCs does not provide the ability to distinguish the individual ADRs ('Preferred Terms', or PTs) reported. Whilst this was not the focus of the current work, the article by Berhe et al. (4) revealed higher reporting of certain ADRs when expressed as PTs (e.g. lip swelling, cough, angioedema) and little of others (e.g. death, myocardial infarction, congestive cardiac failure) when data from Africa are compared with the RoW, an indication once again of the ability of ICSRs to reveal safety differences between Africa and the RoW.

Features of ICSRs: Africa vs. the RoW

There is a difference in the product classes implicated in ICSRs from Africa compared with the RoW. Several factors could account for this, including differences in disease patterns and prescriptions, differences in PV systems and ADR reporting, and differences in health systems and health literacy, amongst others. These issues are impossible to determine from analyses of VigiBase® data. However, an extremely important fact that VigiBase® reveals is that reporting from Africa is extremely low, even for diseases that are more prevalent in Africa. For instance, there were three- to sixfold more ICSRs to nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors and combination antivirals in the RoW than in Africa, even though many more millions of these products are used in Africa than in the RoW. A similar situation occurred in relation to the reporting of ICSRs to antimalarials, as noted by Kuemmerle et al. (6). ICSRs from the RoW were not dominated by any one class of products, an indication of a PV system that looks at all prevailing conditions and medicines used in their management rather than only products for 'public health programmes'. Thus, while antiretrovirals form the top three product classes in African

ICSRs and account for more than 30 % of African reports, the three main product classes from the RoW are TNFa inhibitors, topical nonsteroidal anti-inflammatory agents and selective immunosuppresants. These three product classes account for 9.63 % of all RoW ICSRs. The only product class that was among the top 10 from both Africa and the RoW are interferons (2130 vs. 211,098 ICSRs), an interesting observation considering their usage in a wide range of conditions, including HIV/AIDS-related Kaposi's sarcoma, leukaemia, hepatitis B, and multiple sclerosis, amongst others. HMG CoA reductase inhibitors (statins), antidepressants, nonsteroidal anti-inflammatory drugs and benzodiazepines are poorly represented in African ICSRs. This is not due to the absence of conditions such as hypercholesterolemia, depression, inflammation, insomnia and epilepsy in Africa. Rather, it seems to reflect poor reporting of ICSRs and/or poor prescriptions for products to deal with these conditions, or both. For instance, the work by Berhe et al. (4) found poor reporting of ICSRs to statins, with all but two ICSRs to statins coming from one country (South Africa), which Berhe et al. (4) inferred to probably be due to a focused PV activity by the manufacturer. The main product class implicated in the RoW ICSRs are TNFa inhibitors (including monoclonal antibodies), which are indicated for a wide range of serious life-threatening conditions and are widely used. Several are marketed with 'black-box' warnings requiring reporting of all events to national regulatory agencies. TNFa inhibitors are unlikely to be used by large numbers of people in Africa due to their high cost, and this may explain why they do not feature among the top product classes in African ICSRs.

The only difference in the demography of patients in ICSRs from Africa and the RoW is in relation to age. The subgroup analysis of cardiometabolic drugs undertaken by Berhe et al. (4) found the same difference, which is not surprising considering that the population in Africa is relatively younger compared with the RoW. Females dominate ICSRs in both Africa and the RoW.

The present study has shown that PV in Africa is growing in terms of the number of countries joining the PIDM, as well as the number of ICSRs being submitted. African reports are different from the RoW, offering the possibility of identifying important safety signals, as already mentioned by others (23). However, the absolute numbers of ICSRs in VigiBase® are extremely low. The increasing promotion of other PV methods, including targeted spontaneous reporting and cohort event monitoring (24), could strengthen PV in Africa, while educational interventions and the use of the recent WHO– International Society of Pharmacovigilance (ISoP) PV curriculum (25) should support standardised PV education. Both of these would contribute toward improved ICSR reporting from Africa. The era of countries submitting just the sufficient number of ICSRs to become members of the PIDM would then be a thing of the past, especially if countries could use PV assessment tools such as the WHO PV Indicator and the MSH Indicator-based Pharmacovigilance Assessment Tool (IPAT) to evaluate their own systems and target interventions as appropriate.

Limitations

This study was a review only of the data submitted by national PV Centres to VigiBase®, which may be a tiny fraction of the overall ICSRs in-country. Differences in health systems, prescriptions and disease patterns could also account for several of the differences observed between Africa and the RoW. Unpublished evidence gathered during PV country support missions in Africa suggests that the capacity for data management, including ICSR submission to VigiBase®, is weak; several countries had an appreciable quantity of data stored in various ways (boxes, spreadsheets, etc.), and yet to be submitted to VigiBase®. A significant proportion of ICSRs that are filled out by healthcare professionals remain with national PV centres and are not submitted to VigiBase®. Each ICSR used in the analyses in this study could contain more than one ADR, hence the number of SOCs may be more than the number of ICSRs. The counting of combination products and products that are used concurrently (e.g. the use of highly active antiretroviral therapy) may lead to some products being over-represented in the count of products implicated in ICSRs. Finally, the data were analysed as present in VigiBase®, meaning they contain the essential basic features of reporting (identified patient, product, ADR and reporter) without any assessment of causality or evaluation of the quality of the report.

Conclusions

PV in Africa is in its developing stages, with low numbers of ICSRs reported to VigiBase®. Several countries from Africa have joined the PIDM over the past few years but more than one-third of African countries are still not members of the PIDM. The characteristics of ICSRs from Africa are quite different from those of the RoW in terms of products and types of ADRs reported. African ICSRs are dominated by products for infectious diseases, including HIV/AIDS and antibiotics, while ICSRs from the RoW are mainly in relation to the following classes of products, namely TNFa inhibitors, topical nonsteroidal anti-inflammatory drugs, immunosuppresants, selective serotonin reuptake inhibitors and statins. The dominant age groups in reports from Africa and the RoW also differ, while the gender of patients are nearly identical. With further developments and improvements in PV in Africa, the reporting and submission of ICSRs of good quality to VigiBase® is expected to grow. This will permit signal detection and the utilisation of other proactive methods for safety surveillance of medicines, vaccines and all other medical products to improve patient safety and public health.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interest

Haggar Hilda Ampadu, Jarno Hoekman, Marieke De Bruin, Shanthi Pal, Sten Olsson, Daniele Sartori, Hubert Leufkens and Alexander Dodoo have no conflicts of interest that are directly related to the content of this study.

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CHAPTER 2.2

ORGANIZATIONAL CAPACITIES OF NATIONAL PHARMACOVIGILANCE CENTRES IN AFRICA: ASSESSMENT OF RESOURCE ELEMENTS ASSOCIATED WITH SUCCESSFUL AND UNSUCCESSFUL PHARMACOVIGILANCE EXPERIENCES

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ABSTRACT

Background

National pharmacovigilance centres (national centres) are gradually gaining visibility as part of the healthcare delivery system in Africa. As does happen in high-income countries, it is assumed that national centres can play a central coordinating role in their national pharmacovigilance (PV) systems. However, there are no studies that have investigated whether national centres in Africa have sufficient organizational capacity to deliver on this mandate and previous studies have reported challenges such as lack of funding, political will and adequate human resources.

Objectives

The objective of this paper was to provide insight into activities of national centres that were deemed successful or unsuccessful by their strategic leaders and by assessing whether the attribution of success or failure is associated with particular types of resources or stakeholders.

Methods

We conducted interviews with strategic leaders in national centres in 18 African countries, to examine how they link the capacity of their organization to the outcomes of activities coordinated by their centres. Strategic leaders were asked to describe three situations in which activities conducted by their centre were deemed successful and unsuccessful. We analysed these experiences for common themes and examined whether strategic leaders attributed particular types of resources and relationships with stakeholders with successful or unsuccessful activities.

Results

We found that strategic leaders most often attributed successful experiences to the acquisition of political (e.g. legal mandate) or technical (e.g. active surveillance database) resources, while unsuccessful experiences were often attributed to the lack of financial and human resources. Stakeholders that were most often mentioned in association with successful experiences were national government and development partners, whereas national government and public health programmes (PHPs) were often mentioned in unsuccessful experiences. All 18 centres, regardless of maturity of their PV systems had similar challenges.

Conclusions

The study concludes that national centres in Africa are faced with 3 core challenges: (1) over-reliance on development partners, (2) seeming indifference of national governments to provide support after national centres have gained membership of

the World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) and (3) engaging public health programmes in a sustainable way.

Keywords

National pharmacovigilance centres; Organizational capacity; Resource elements; Stakeholders; Outcomes; National governments; Development partners; Public Health Programmes

INTRODUCTION

The last years have witnessed increasing efforts in low and middle income countries to establish formal national pharmacovigilance centres (national centres) with several of these in sub-Saharan Africa (1,2). Pharmacovigilance (PV) became an important discipline in the 1960s following the thalidomide tragedy (3). The realization that the tragedy could have been prevented if countries collected and shared data on medicine safety led the World Health Organization (WHO) decision-making body i.e. the World Health Assembly to issue a resolution inviting "Member States to arrange for a systematic collection of information on Serious Adverse Drug Reactions (ADR) observed during the development of a drug and, in particular, after its release for general use"(4). In response to this call, national governments around the world established national pharmacovigilance centres to coordinate medicine safety surveillance efforts. Over the years these centres have become key organizations involved in initiating, building and sustaining efforts for safety surveillance (5). Particularly in high income countries, national centres now function as central nodes for national PV efforts and they contribute to building national PV systems by collaborating with other stakeholders be they local, national or international (2,5,6).

There is a widespread expectation among several stakeholders including the WHO that national PV systems need to be driven by a national centre (7). However, previous studies have noted that most national centres in sub-Saharan Africa are currently not the central coordinating bodies of PV efforts in their respective countries (8). A study by Maigetter et al (9) revealed that in many countries in Africa, PV functions are not conducted within a separate organization but lumped together with other regulatory functions such as medicines registration, licensing of premises and inspections. The national centre is sometimes a desk in the national medicines regulatory authority (NMRA) with one or two people assigned to carry out all its functions (1), (8), (10) . It is therefore not surprising that the few studies on the features of pharmacovigilance in Africa have arrived at the same conclusion that PV activities performed by African national centres are limited and beset with several challenges of which overcoming a lack of resources is one of the most prominent (1), (11), (12). This is very different from the situation in developed countries where the national centre is an integral part of the public health system and plays a key role in implementing the national PV agenda. (13).

However, there is also evidence that the development of PV systems has become a key priority in certain countries which has led to successes. For instance, the Ghana Food and Drugs Authority has implemented legal provisions mandating Marketing Authorisation Holders (MAHs) to have a Qualified Person for Pharmacovigilance (QPPV) in line with the Public Health Act of Ghana (Act 851, 2012; Part Seven) (14). The Pharmacy and Poisons Board of Kenya has been designated as a Regional Centre of Regulatory Excellence (RCORE) in pharmacovigilance by the African Union through

the African Medicines Regulatory Harmonization (AMRH) programme (15). Despite this attention, our knowledge on the role and experiences of national centres in Africa is limited especially as it relates to the organizational capacity (resources and relationships) they need to deliver on their mandate. We fill this knowledge gap by providing insight into the activities of national centres that were deemed successful and unsuccessful by the strategic leaders of the centre and by assessing whether the attribution of success or failure is associated with particular types of resources or stakeholders.

National PV centres and PV initiatives

National PV centres

The WHO defines a national centre as a single, government-designated centre within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all aspects related to drug safety (16).The functions (16), (17) of a national centre include, but are not limited to:

- Coordinating of pharmacovigilance activities nationwide;
- Creating awareness on pharmacovigilance among health professionals, healthcare providers, marketing authorization holders and the public;
- Post-marketing surveillance of regulated products;
- Establishing and maintaining a functional national database on ADRs and other medicine related problems to identify unknown or poorly specified adverse effects;
- Leading national and international collaboration on safety issues
- Contributing to the fight against counterfeit medicines

It is obvious from the above that national centres in Africa have a broad mandate and thus require adequate resources to undertake these tasks and to coordinate their national PV systems. The available evidence however suggests that the PV landscape in many African countries is dominated by fragmented PV initiatives and programmes rather than a well-coordinated national PV system (18).

PV initiatives and programmes

On the African continent, PV activities are often undertaken within public health programmes (PHP) that are executed by the Ministry of Health either alone, or more often, in collaboration with external development partners. Global health initiatives

such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the US Presidents Malaria Initiative, Global Fund Against HIV/AIDS, TB and Malaria (Global Fund), The Bill and Melinda Gates Foundation's Malaria Eradication and the adoption of the millennium development goals by the United Nations in the 2000s provided funding for several African countries to combat priority diseases (12), (19), (20). To qualify to receive this funding, national governments, specifically the Ministries of Health, were tasked to establish formal disease control programmes also known as public health programmes in collaboration with WHO. These programmes were placed under the disease control department of the Ministries of Health and include well known programmes such as the National AIDS/HIV Control Programme, National Tuberculosis Control Programme, National Malaria Control Programmes, the Expanded Programme on Immunization and the lesser known programmes such as the Neglected Tropical Diseases programme. Typically, the programme administrators will draft joint work plans with the development partners providing the funding.

The execution of PHPs resulted in increased access to medicines in African countries but at the same time led to a realisation that safety monitoring systems were largely absent in these countries. This led to calls from the WHO for collaboration among stakeholders to ensure that these countries develop pharmacovigilance systems to protect their populations from medicinal product associated harms (21). Typically, NMRAs were tasked to collaborate with these PHPs to ensure safety monitoring. As part of this endeavour, several nations in Africa established national centres. The increased funding for PHPs thus was instrumental in the establishment of some national centres in Africa. Most of the established national centres were positioned as individual departments in the NMRA and most still reside within the Ministry of Health (9). National centres rely on the national government to provide resources for operations, making the national government their most important stakeholder (11). National centres are also dependent on healthcare professionals, the pharmaceutical industry, academia, PHPs, intergovernmental organizations and development partners who may provide resources to achieve outcomes. Public health programmes rely on spontaneous ADR reporting as the bedrock for collecting safety data on the products used in these programmes and collaborate with the national centres by submitting ADRs directly to the national centres. Sometimes, the national centres also contribute to joint mass drug administration campaigns like deworming of school children with the PHPs through collection and monitoring of ADRs for the safety of patients.

METHODS

This was a qualitative, investigator-administered, semi-structured interview study of strategic leaders in 18 out of 36 national centres in Africa to provide insight into the resource elements, relationships and outcomes they associate with successful and unsuccessful pharmacovigilance experiences.

Selection

The participants were purposely selected taking into consideration language (English, French and Portuguese) and region (Central, East, West and Southern Africa) representing sub-Saharan Africa as seen in Figure 1. To be included in the study, individuals needed to be a current or immediate past employee of a national centre and to be employed in a decision-making role. Sixteen of those interviewed are/were the heads of the national centre in their respective countries.

Data collection

Interviews were conducted between September 2015 and April 2016. Sixteen interviews were conducted face-to-face and two via phone calls and followed up by emails. The lead investigator had preliminary meetings with participants, explained the research aims and sought verbal consent. Each participant was subsequently

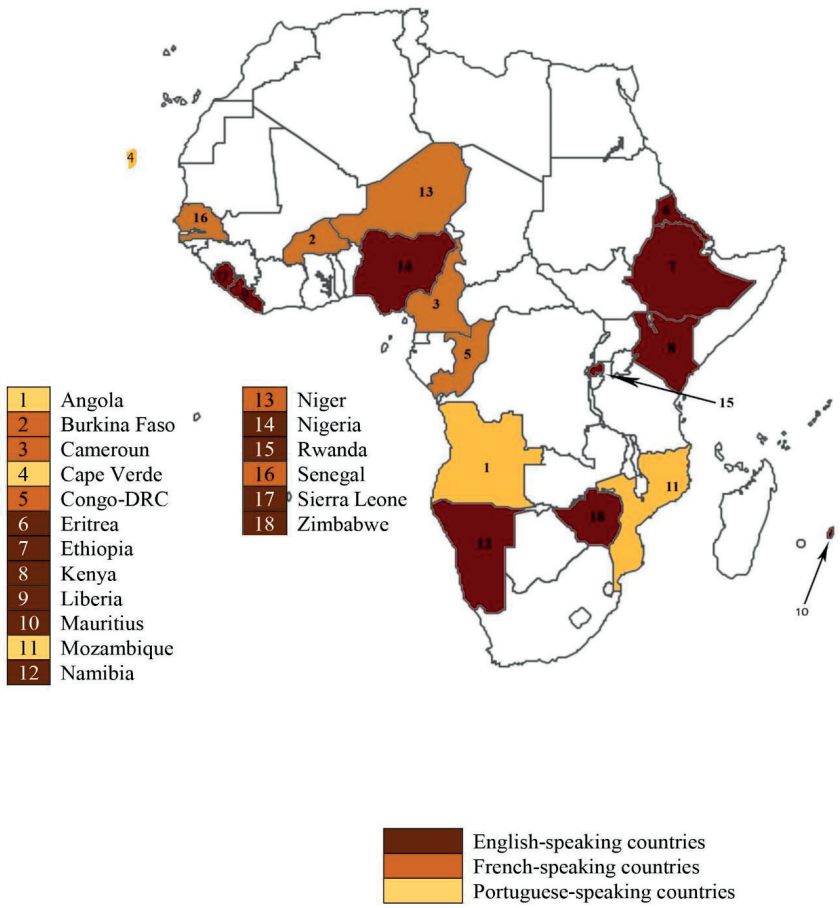

Figure 1. Countries, regions and languages of participants

interviewed once, with interview duration ranging between 15-25 minutes. The Ghana Health Service Ethics Review Committee's Standard Operating Procedure, mentions that ethical review is not needed for studies documenting "public behaviour" of professionals working in a public organization (22). Accordingly, we did not seek ethical approval for this study but conformed with ethical guidance on anonymization of quotes to prevent statements that could be traced back to individuals.

Two pilot interviews led to minor tweaks of the interview protocol and are included in the final data analysis. An interview guide is provided in appendix A. In short, participants were asked to describe pharmacovigilance experiences defined as an activity in which the national centre was involved and that had an impact on the delivery of the mandate of the centre as defined in section 2.1. The interviewer asked for three successful and unsuccessful experiences defined as experiences that had a positive or negative impact on mandate delivery, respectively. For each situation the interviewer also asked for reasons why the experience was deemed successful or unsuccessful and asked follow-up questions when needed.

We subsequently analysed these situations to examine how the strategic leaders attributed positive or negative impact to:

a. various types of resources (e.g. financial, technical, human, social, political resources) they acquired and how they used them in programme and process management;

b. creation and maintenance of relationships with different types of stakeholders (e.g. national government, development partners, intergovernmental organizations, industry, academia, public health programmes)

Thus, a successful experience was defined as national centre relationship with a stakeholder that resulted in the attainment of a resource. An example is if a national centre was able to lobby the Ministry of Health/Minister of Health to present a case in parliament to get a bill passed for Marketing Authorization Holders to be held responsible for the safety of their products on the market. Consequently a negative experience was defined as any national centre relationship with a stakeholder that did not result in the attainment of a resource. An example is if a national centre is not able to embark on a nationwide training of healthcare workers on ADR reporting because it doesn't have a budget allocation for such an activity from the national government.

Coding

Interviews were transcribed verbatim by an experienced co-author (DA). Upon compilation, a total of 18 *3= 54 successful and 54 unsuccessful experiences were derived. Each experience was subsequently coded for mentioned relationships with stakeholders, mentioned acquired resources and mentioned outcomes. For instance:

if a national centre described an experience where they were able to lobby the Ministry of Health/Minister of Health to present a case in Parliament to get a law passed for Marketing Authorization Holders to be held responsible for the safety of their products on the market, the experience was coded as a relationship with the Ministry of Health/ Minister of Health, the acquired resource was legal backing and the function was post-marketing surveillance of regulated products. Conversely, a negative experience was defined as any national centre relationship with a stakeholder that did not result in the attainment of a resource. An example is if a national centre was not able to embark on a nationwide training of healthcare workers on ADR reporting because it doesn't have a budget allocation for such an activity from the national government. The stakeholder mentioned in this case was national government, the resource not provided was financial resources and the function not delivered was creating awareness on pharmacovigilance.

An initial coding of 9 transcribed texts was done manually per participant by the lead investigator (HHA) and reviewed by two authors (JH, AD). For each experience, resources mentioned were assigned to one of 5 resource categories, stakeholders associated with the acquisition of these resources were assigned to one of 6 stakeholder groups and functions fulfilled or not fulfilled were assigned to one of 6 groups. Definitions for each resource and stakeholder groups are provided in Table 1, whereas the six functions of national centres are mentioned in section 2.1. We only considered one dominant resource and stakeholder per experience. In 12 experiences, participants did not mention the stakeholders associated with

Table 1. Definitions of resources and relationships used in the study

Type of resource	Definition
Financial resources	Funding or financial capital
Technical resources	Materials and infrastructure (e.g. computers, phones)
Political resources	Law, policy and other legislative instruments
Human resource	Staff and knowledge
Social resource	Relationships including collaborations, partnerships and networks
Type of stakeholder	
National government	The National Regulatory Agency and the Ministry of Health
Development partners	Organizations that work with a variety of in-country partners to improve the lives of poor and vulnerable people in developing countries
Inter-governmental organizations	Organizations comprising mainly of sovereign states
Public health programmes	Organizations responsible for health services to improve and protect community health
Academia	Organizations concerned with the pursuit of education, research and scholarship
Industry	Organizations who market and sell pharmaceutical products

the resources. Upon completion 108 resources and 96 stakeholders were coded for the combination of successful and unsuccessful experiences. The list of generated codes was compared to the remaining 9 transcribed texts, but no new categories or themes emerged.

2.2 Analysis

The coded interview data was tabulated using frequency tables. Successful and unsuccessful experiences were assessed for frequently mentioned combinations of resources, stakeholders and functions. The combinations of resources, stakeholder and functions that strategic leaders attributed to success or failure were described as themes with verbatim quotes from the participants.

National centres in Africa are at varying levels of maturation thus we also compared experiences within country-groupings using the grouping system developed by Management Sciences for Health (MSH) (6). According to this, Angola, Burkina Faso, Cameroun, Cape Verde, Eritrea, Liberia, Mauritius and Niger are in group 1 - countries with minimal or no capacity for PV. Rwanda, Congo-DRC, Ethiopia, Kenya, Mozambique, Senegal, Sierra Leone and Zimbabwe are in group 2- countries with basic organizational structures. Group 3 countries are countries with the capacity to collect and evaluate safety data based on legal and organizational structure; none of the countries interviewed were in group 3. Namibia and Nigeria are in group 4 - countries that have basic structures for both passive and active surveillance activities. Statistical analysis was not performed.

RESULTS

Of the 18 participants, there were 8 females and 10 males. Fifteen were pharmacists and 3 were physicians. All the 18 national centres interviewed (except one) were departments under the NMRA.

Table 2 provides an overview of the MSH country groupings and the different types of successful and unsuccessful experiences mentioned by participants and the coded resources based on each experience. Figure 2 depicts the dominant stakeholder groups mentioned in association with these resources. Of the 108 experiences collected, participants most often discussed experiences related to the acquisition of technical resources (16/54) such as reporting infrastructure, testing laboratories, phones and vehicles, and political resources (13/54) such as legal mandate, decentralization and political support as successful. Financial resources (15/54) such as grants and dedicated budgets as well as human resources (13/54) such as staffing, capacity building, knowledge were most often described as unsuccessful. Stakeholders that were most often mentioned in experiences by participants were national government (50/108), development partners (16/108) and public health programmes (16/108). The resources and stakeholders associated with these experiences are elaborated on below starting from the most frequently mentioned.

Table 2. MSH Country Groupings, Experiences and Resources

Country	Successful Experiences	Successful Resources Assigned	Unsuccessful Experiences	Unsuccessful Resources Assigned
MSH Group 1- Countries with minimal or no capacity for PV				
Angola	• Deployment of PV focal persons to various regions of the country, thus decentralizing PV • ADR reports received through positive collaboration with HIV and Malaria Programmes • Funds received through collaboration with development partners	• Political resource • Social resource • Financial resource	• No PV law to enforce regulations • No dedicated budget for PV • No reporting tools	• Political resource • Financial resource • Technical resource
Burkina Faso	• Regulatory framework implemented by government • Deployment of PV focal persons to various regions of the country, thus decentralizing PV • Establishment of national technical committees with tools for PV work	• Political resource • Political resource • Technical resource	• No properly recognized National Regulatory Authority • No dedicated budget for PV • No tools to embark on active monitoring	• Political resource • Financial resource • Technical resource
Cameroon	• Funds received through collaboration with development partners • Continuous receipt of PV literature through established relationship with development partners • PV Decree signed by head of state and minister of health	• Financial resource • Social resource • Political resource	• No dedicated budget for PV • Untrained PV staff • No internet to submit ADR data to VigiFlow	• Financial resource • Human resource • Technical resource

Table 2. (continued)

Country	Successful Experiences	Successful Resources Assigned	Unsuccessful Experiences	Unsuccessful Resources Assigned
Cape Verde	• Deployment of PV focal persons to various regions of the country, thus decentralizing PV • Improved reporting infrastructure through TV and radio campaigns • Dissemination of ADR data through publication in peer review journals for Portuguese speaking countries	• Political resource • Technical resource • Technical resource	• No PV law to enforce regulations • Inadequate reporting infrastructure • No dedicated budget for PV	• Political resource • Technical resource • Financial resource
Eritrea	• Funds received through collaboration with development partners • Trained PV staff • Deployment of PV focal persons to various regions of the country, thus decentralizing PV	• Financial resource • Human resource • Political resource	• No PV law to mandate reporting by industry • Low AEFI reporting due to poor collaboration with EPI • Pharma industry does not monitor the safety of their products	• Political resource • Technical resource • Political resource
Liberia	• Trained PV staff • Incorporation of PV into curriculum of educational institutions due to effective collaboration with Academia • Availability of tools for active monitoring of drugs from international donors	• Human resource • Social resource • Technical resource	• No dedicated budget for PV • Inadequate human resource for PV activities • No PV law to enforce regulations	• Financial resource • Human resource • Political resource
Mauritius	• Full membership in the PIDM due to positive collaboration with WHO • Improved reporting infrastructure through collaboration with PHPs • Technical support received through collaboration with development partners and PHPs	• Social resource • Technical resource • Social resource	• Inadequate reporting infrastructure • No dedicated budget for PV • No PV law to enforce regulations	Technical resource Financial resource Political resource

Table 2. (continued)

Country	Successful Experiences	Successful Resources Assigned	Unsuccessful Experiences	Unsuccessful Resources Assigned
Niger	• Deployment of PV focal persons to various regions of the country, thus decentralizing PV • Attending trainings with the Head of the NRA, facilitation of travel by Head of NRA • Tools available to embark on district inspections	• Political resource • Political resource • Technical resource	• Inadequate human resource for PV activities • Untrained PV staff • No dedicated budget for PV	Human resource Human resource Financial resource
MSH Group 2- Countries with basic organizational structures for PV				
Congo-DRC	• Technical support received through collaboration with development partners and PHPs • Introduction of android smartphones to communicate effectively with health practitioners • More trained human resource from Implementation of Drug Therapeutic Committees(DTC)	• Social resource • Technical resource • Human resource	• Inadequate reporting infrastructure • Untrained PV staff • No dedicated budget for PV	Technical resource Human resource Financial resource
Ethiopia	• Trained PV staff • Introduced PV into national curriculum, to train more human resource for PV • Fulltime MSH employee placed at the national centre to help with PV activities	• Human resource • Human resource • Human resource	• Lack of accredited laboratorial • More human resources are needed to deliver on mandate • Poor AEFI reporting infrastructure	Technical resource Human resource Technical resource

Table 2. (continued)

Country	Successful Experiences	Successful Resources Assigned	Unsuccessful Experiences	Unsuccessful Resources Assigned
Kenya	• Two ministers of state took part in the launch of the PV system. • Launch of online pharmacovigilance electronic reporting system • Funds provided through joint post market surveillance with PHPs	• Political resource • Technical resource • Financial resource	• More human resources are needed to deliver on mandate • Inadequate reporting infrastructure • No PV law to enforce regulations	Human resource Technical resource Political resource
Mozambique	• Deployment of PV focal persons to various regions of the country, thus decentralizing PV • Funds for training received through collaboration with WHO • Availability of legal instruments to promote PV	• Political resource • Financial resource • Political resource	• Untrained PV staff • No dedicated budget for PV • Poor collaboration with PHPs	Human resource Financial resource Social resource
Rwanda	• Trained PV staff • Implemented performance based evaluations for district hospitals • Collaboration with AMRH and EAC-PV harmonization to promote PV activities	• Human resource • Technical resource • Social resource	• Inadequate human resource for PV activities • No dedicated budget for PV • Poor collaboration with PHPs	• Human resource • Financial resource • Social resource
Senegal	• Trained PV staff • Tools available for data analysis and data sharing • Funds for training received through collaboration with NMCP	• Human resource • Technical resource • Financial resource	• No PV staff with data management expertise • No PV representatives in the regions of the country, only the capital region • No dedicated budget for PV	• Human resource • Political resource • Financial resource

Table 2. (continued)

Country	Successful Experiences	Successful Resources Assigned	Unsuccessful Experiences	Unsuccessful Resources Assigned
Sierra Leone	• Adjustment of malaria treatment due to strong collaboration with NMCP • Deployment of PV focal persons to various regions of the country, thus decentralizing PV • Introduced PV into national curriculum, to train more human resource for PV	• Social resource • Political resource • Human resource	• No dedicated budget for PV • Inadequate reporting infrastructure • No PV law to enforce regulations	• Financial resource • Political resource • Political resource
Zimbabwe	• Donor funding available for PV related projects • Guidance documents and publications available for PV work • AEFI Surveillance systems established since 2001	• Financial resource • Technical resource • Technical resource	• No internet (Wi-Fi) services to submit data to VigiBase • Inability to generate own funds • Inadequate human resource for PV activities	• Technical resource • Financial resource • Human resource
Group 4- Countries with basic structures for passive and active surveillance				
Namibia	• Ministry of Health gave the mandate to setup the national centre • Active surveillance tools available for safety monitoring • Implemented patient reporting system	• Political resource • Technical resource • Technical resource	• Inadequate human resource for PV activities • No dedicated budget for PV • Inadequate spontaneous reporting infrastructure	• Human resource • Financial resource • Technical resource
Nigeria	• Active surveillance tools available for safety monitoring • Funds for training received through collaboration with PHPs • Guidance documents and publications available for PV work	• Technical resource • Financial resource • Technical resource	• No online reporting infrastructure • Inadequate human resource for PV activities • No PV law to enforce regulations	• Technical resource • Human resource • Political resource

Group 1: Countries with minimal or no capacity for PV; **Group 2**: Countries with basic organizational structures; **Group 3:** Countries have the capacity to collect and evaluate safety data based on legal and organizational structures; **Group 4**: Countries that have basic structures for both passive and active surveillance activities.

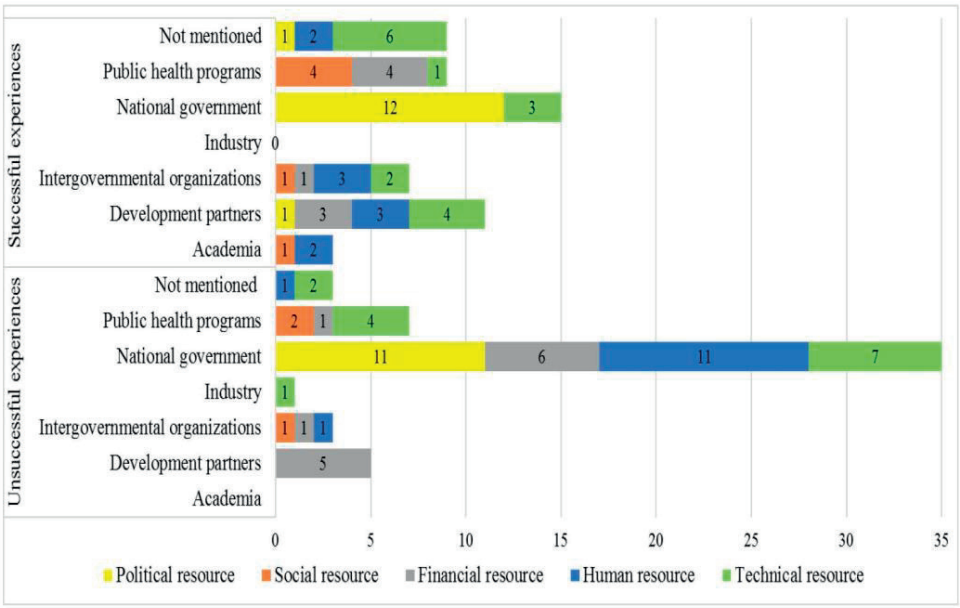

Figure 2. Stakeholders mentioned in the provision of resources by participants

Experiences involving technical resources

The interviewees mainly made reference to technical resources that facilitated ADR reporting. For instance, participants mentioned that having access to online reporting systems made data readily available and had other benefits.

> *Launching of the online reporting system has helped, it minimizes the paperwork and it is less tedious than the manual reporting. (Participant 8)*

Reference was also made to technical resources for day-to-day operations. For instance, having vehicles aided post-market surveillance and in mentioning the benefits of acquiring smartphones, a participant mentioned:

> *We found that doctors have a problem managing serious ADRs in the field. Our smartphone application allows us (national centre) to communicate with doctors in real time. (Participant 5)*

In discussing inability to acquire technical resources, lack of data analysis tools, internet, data management infrastructure and accredited laboratories were emphasized.

We have only one national laboratory; we are not able to test samples to verify if they are standard or counterfeit when ADRs are reported to us. (Participant 7)

Stakeholders: Participants expected to acquire basic technical resources such as computers and internet needed for their day to day work from national governments and costly ones from PHPs or development partners.

I have ICSRs, but can't enter into VigiFlow because we don't have internet connection all the time. (Participant 3)

National governments were more often associated with unsuccessful acquisition of technical resources and development partners the most successful acquisition of technical resources.

Participants indicated that they work closely with development partners in their day to day work whether in the provision of tools needed for their work or in the provision of other technical resources.

MSH was instrumental in setting up the national centre. They provided technical resources and then later the national centre was incorporated into the structure of the ministry. (Participant 12)

National government was lauded for providing space in the national regulatory authority for the national centre and setting up technical committees.

The government has set up national commission with tools to validate ADR reports, they have the authority to withdraw or suspend any medicine from the country. (Participant 2)

A recurring unsuccessful acquisition of technical resources associated with public health programmes was the inability to deploy mutual surveillance systems between the programmes and the centre to enable efficient data sharing.

Vaccine surveillance system is not in place at all at the national centre and the extended programme for immunization, we are currently working on the establishment of such a vaccine surveillance system. (Participant 6)

It was mentioned that PHPs sometimes only provided disease-specific resources. For example, a vaccine surveillance system can only fulfil a specific need of a national centre's mandate and may not be useful for other purposes which leads to national centres having silo surveillance systems as the interviews revealed. Further, it was mentioned that development partners provided technical resources based on their programme objectives. Participants expressed that they tie their work plans to development partners' agenda even when their needs were different.

Working with development partners is sometimes difficult because they decide what level to tie their resources and sometimes the resources are not specific for our needs. (Participant 9)

MSH Country groupings: It was expected that countries in group 4 would discuss more sophisticated technical resources, however the interviews revealed that countries with different levels of maturation of their PV system discussed similar technical resources. In discussing unsuccessful acquisition of technical resources, two countries in group 4 with basic structures for both passive and active surveillance activities were for instance struggling with online reporting:

The issue of reporting online for instance; for some strange reason we haven't been able to do something as simple as that. (Participant 14)

At least one country in each group mentioned successful acquisition of technical resources from development partners. Countries in groups 1 and 2 appear to work more closely with the Global Fund whereas countries in group 4 work with a more varied group of development partners (e.g. John Snow Incorporated (JSI) and United States Pharmacopeia (USP).

Experiences involving political resources

Political resources such as launching of the pharmacovigilance system by the Minister of Health was used to champion pharmacovigilance to other health professionals and the public. Political support sometimes manifested in the Ministers of Health accompanying national centre personnel on awareness creation campaigns which helped legitimize the national centre as an organization in the healthcare system.

Experiences in which legal mandates were utilized to withdraw harmful products, decentralize PV activities and mandate reporting by industry were also mentioned.

Regarding common successful experiences, three out of the 18 strategic leaders interviewed indicated they had a legal framework or law that specifically mentions pharmacovigilance and a participant described how empowering it can be:

The national centre was set up under the NRA with legal framework, guidelines, staff, advisory committee and reporting systems through consultation with all stakeholders. (Participant 18)

Other common successful experiences related to decentralization which seeks to bring pharmacovigilance closer to the patient. Six of the countries interviewed had embarked on decentralization initiatives by establishing regional or zonal centres, sometimes by using Drug Therapeutics Committees (DTCs) in regional public hospitals as was the case in Congo-DRC and Eritrea or by having regional focal persons as was the case in Angola, Cape Verde, Mozambique and Sierra Leone.

With the support of the national government, we introduced pharmacovigilance ambassadors in all 4 regions of our country and this has helped increase ICSR reporting. (Participant 17)

Unsuccessful experiences when discussing political resources centered on lack of legislations, inability to amend existing Health Bills to include PV and inability to mandate reporting by industry. Five of the countries interviewed had processes in place to implement laws.

Pharmacovigilance is not developed in my country because the processes to implement PV law started in 2003 and is ongoing as of 2015. (Participant 1)

Participants stated they have had to improvise in the absence of specific PV laws by relying on PV statements in the national regulatory authority laws as legal backing for their work.

We have the regulatory authority act which states to ensure safety of products; it sets the pace that this is the intention of government to eventually enact a PV law. (Participant 14)

Stakeholders: As expected, almost all the political resources were associated with national government. Participants emphasized that only national governments can provide national centres with legitimacy. Successful acquisition of political resources from national government and the accompanying legitimacy was considered an enabling condition which allowed the national centre to mobilise other resources and have stable operations. However, several participants mentioned not having full political backing as an unsuccessful experience. The interviews revealed that in a considerable number of cases, national governments provided initial political resources by enacting policies which aided national centres to become members of the WHO Programme for International Drug Monitoring (PIDM) but failed to continue with this. This also required the national government to launch the national pharmacovigilance system. It is important to note that many successful experiences to do with the acquisition of political resources focus on early stages of the PV system development when legal systems were still being built and new policies being implemented.

To start pharmacovigilance, the government adopted two regulatory frameworks; one formed the regulatory authority and the second formed the national centre. These two documents helped start pharmacovigilance activities in the country. (Participant 2)

Most participants had challenges with the acquisition of political resources from the national government.

In the absence of strong regulatory laws, our country has become a dumping ground of fake products. The current law does not specify pharmacovigilance activities making it difficult to prosecute offenders. (Participant 9)

MSH Country groupings: Countries in group 4 spoke of receiving varied resources from government whilst countries in groups 1 and 2 spoke mainly of political support they have received.

I came to this meeting with my Director. She is 2nd to the Minister of Health and she facilitated everything. (Participant 13)

Irrespective of level of maturation of the PV system, interviewees referred to the absence of specific pharmacovigilance laws when discussing unsuccessful

acquisition of political resources. Moreover, none of the countries had autonomous centres. It was unexpected that some countries in group 4 are still working with acts that reference pharmacovigilance and not PV-specific laws.

We are not an autonomous agency. The whole idea of our national regulatory agency set up was to remove government bureaucracy so that we can do drug regulation without all those levels of reporting to slow us down. (Participant 14)

Experiences involving financial resources

There were 23 experiences (8 successful, 15 unsuccessful) mentioning financial resources (Table 2). The dominant stakeholder groups associated with financial resources were development partners (8), national government (6) and public health programmes (5). Most of the national centres interviewed were not income-generating and got their funding from projects and/or from government budgets. Fourteen of the eighteen countries stated they did not have dedicated budget for PV activities. Successfully attained financial resources were used to acquire other resources, mainly technical and human resource. Participants discussed buying equipment for day-to-day operations (e.g. computers) and sending national centre personnel to international meetings. Experiences describing lack of financial resources focused mainly on irregularity of funding and lack of autonomy of national centres to generate their own revenue. The interviews revealed that the lack of a stable financial resource stream manifested itself in several ways: firstly, the national centre was not able to undertake key activities such as ICSR collection. Secondly, they are unable to embark on important initiatives such as active monitoring and lastly, national centre personnel are unable to acquire much needed training necessary for their work. Five of the strategic leaders who indicated they were successful in acquiring financial resources also indicated they were unsuccessful in acquiring financial resources usually because some of their efforts didn't yield results.

The inability to generate own revenues was considered particularly problematic when it increased dependency on the government:

We are totally dependent on the Ministry; we do not generate our own income hence we are limited in the number of activities we can undertake. (Participant 9)

The national centre does not have the autonomy to submit its own budget to the national regulatory authority. (Participant 16)

I don't belong to the group who discuss budget, it's the director (of the NRA), I can propose activities, but the director decides whether we do it or not. (Participant 3)

Stakeholders: Development partners appeared to play a key role in the provision of financial resources (8/21) but many participants (5/8) mentioned that they are not always able to acquire funding from them. This might be explained by the fact that national centres have typically enjoyed financial resources from development partners which has become part of their resource acquisition strategy.

Some participants elaborated on successful acquisition of financial resources from development partners

We receive donor funding for PV projects. 50% of our staff are funded by donor projects. (Participant 18)

We got financial support from United States Pharmacopeia (USP) and United States Agency for International Development (USAID) to conduct minilabs for malaria and post market surveillance for HIV. (Participant 8)

Fear of losing funding, partners not delivering promised funds and funding tied to partners' goals were some of the concerns expressed by participants in discussing inability to acquire financial resources.

Now we are working well with Global Fund but if tomorrow there is no commitment between Global Fund and the country, our activities will be let down. This is a fear I have. (Participant 5)

Discussions on difficulties with acquiring financial resources from national government centred around the unpredictability of funding which hindered planning and forecasting and general inadequate funding to support day to day operations.

(Financial) resources are not very predictable. It takes a lot of efforts to have a budget and still the budget is not enough for our priority activities. (Participant 4)

National government was not mentioned in association with the successful acquisition of financial resources because participants had tacit expectations that funding for national centres activities is an action that governments should routinely undertake.

MSH Country groupings: Participants in groups 1 and 2 discussed the lack of financial resources from national government for basic operations whilst participants in group 4 appear to have stable funding streams.

Our funding previously was from donors but now we have funding from government and it is based on our activity plan. (Participant 12)

Participants in groups 1 and 2 discussed acquiring financial resources from PHPs and development partners to embark on awareness creation and training. National governments (6/13) and development partners (5/13) were mentioned most in association with unsuccessful acquisition of financial resources by all groups as seen in Figure 2.

Experiences involving human resources

Human resource was mentioned 22 out of 108 times, most often (13/22) in relation to unsuccessful experiences (Table 2). The stakeholder groups mentioned in association with human resource were national government (11/20), intergovernmental organizations (4/20) and development partners (3/20) (Figure 2).

Successful experiences in acquiring human resources were about using experts from Drug Therapeutic Committees (DTCs) to do PV work, having regional focal persons and incorporating PV into the curriculum of health disciplines.

Adequate staffing appears to be a challenge for most national centres. In some cases, national centres had to rely on personnel from other departments to offer support in addition to their regular duties (4/13) and, due to competing priorities, PV activities were compromised.

I have no time to do PV. In the Direction of Pharmacy (national regulatory authority), we have only 6 personnel for all the work and I have other activities to do. (Participant 13)

Moreover, participants emphasized the high personnel turnover at national centres (3/13), such as national centre personnel leaving to go work with development partners, industry and academia because these offer stable work environments.

If you train 10 people today, one or two years later only 2 will still be working, the rest disappear to the other organizations. (Participant 5)

Politics appears to play an important role in the sustainability of national centre personnel as most strategic positions at the national regulatory authority are occupied by political appointees thus affecting who is nominated as head of the national centre. Whilst participants did not state this explicitly, 3 participants provided strong hints.

In Africa most issues are politicized; there have been changes in the system that has weakened the progress we have made in (PV) so far. (Participant 9)

Stakeholders: National government was associated most with unsuccessful experiences in discussing the inability to acquire human resources (11/13). Participants mentioned challenges such as unavailability of skilled expertise. The interviews revealed that some national centres have collected ICSR data but due to a lack of data analysis expertise have not been able to make decisions out of this data.

We use the WHO Method (for causality assessment) but we cannot analyse the data with VigiFlow. We need training. (Participant 16)

National centres are tasked with monitoring the safety of products sold by MAHs. However, the MAH personnel tend be more knowledgeable in PV than national centre personnel. There have been instances where national centres have received documentations from MAHs and have had to rely on the MAHs to explain what the national centre needs to do with such documentation.

MAHs sometimes know more about pharmacovigilance than you who is the regulator. It has been a challenge to build the capacity of the national centre staff to regulate the MAHs. (Participant 14)

Successes in acquiring human resource were mainly associated with development partners (3 experiences), intergovernmental organizations (3 experiences) and academia (2 experiences). Development partners helped with creation of DTCs, staff augmentation and training.

With help from MSH we implemented DTCs in general hospitals to advice the national centre. (Participant 5)

We have a full-time MSH staff placed at the national centre. She is supported by MSH. (Participant 7)

Intergovernmental organizations were mentioned in relation to capacity-building guidelines and other policy documentations development and human resource benefits from belonging to regional partnerships such as the East African Community (EAC).

The EAC harmonization provides us with various expertise from the different countries, for instance we are the lead in Pharmacovigilance whilst other functions such as medicines registration are performed by different countries. (Participant 8)

MSH Country groupings: Lack of adequate human resources both in personnel and expertise was a common theme amongst all three groups. Participants in groups 1 and 2 mentioned not having enough personnel to perform day to day duties whilst participants in group 4 mentioned not having adequate expertise to do active surveillance. Successful acquisition of human resources by groups 1 and 2 were mostly about using the DTCs to augment their operations.

Participants in groups 1 and 2 also mentioned academia as helping augment human resources by incorporating PV into the curriculum of healthcare disciplines.

Experiences involving social resources

Social resources were mentioned 9 out of 108 times and mainly in association with successful experiences (8/9) (Table 2). The stakeholder groups associated with social resource were public health programmes (6/9), intergovernmental organizations (2/9) and Academia (1/9).

The interviews revealed that national centres constantly seek resources from various stakeholders thus being able to build linkages is key to their survival. Social resources such as collaborations, building partnerships, establishing trust-based relations and networking therefore emerged as a separate theme in successful and unsuccessful experiences.

National centres discussed experiences in which they have been able to build mutually respectful trust-based relationships with some organizations which became instrumental in safety monitoring efforts:

Through our strong collaboration with the malaria programme, we embarked on joint monitoring and with the evidence collected we switched our first line of malaria drug from Artesunate+Amodiaquine to Artemether-Lumefantrine. (Participant 17)

Networking with other national centres were also discussed by some participants as beneficial in exchanging knowledge and best practices. Further, PIDM membership guarantees access to publications and advisory support from the WHO, Uppsala Monitoring Centre and the WHO Collaborating Centres in Ghana and Morocco.

Stakeholders: Public health programmes were most often associated with successful acquisition of social resources (4/6) Figure 2. The interviews revealed that PHPs tend to be well-resourced and use medicines or vaccines in their operations thus making them a key stakeholder to national centres. Some PHPs initiated pharmacovigilance activities in some countries.

In 2009 the immunization programme embarked on MenAfriVac vaccination campaign. Our country took advantage of this to start some pharmacovigilance activities. (Participant 13)

By virtue of the huge doses of medications administered in public health programmes they tend to be a gold mine for ICSR data.

We have good collaborations with malaria, tuberculosis and HIV programmes; majority of our ADRs are from the three programmes. Every quarter we share a report with the programmes, so they can appreciate their contributions. (Participant 8)

Successful acquisition of social resources from academia were about working with the universities to incorporate PV in the curricula of healthcare disciplines.

We have developed a framework with the universities to incorporate PV into the teaching of medicine, pharmacy and nursing. (Participant 7)

Finally, a participant indicated that they are encouraged by invitations to conferences and meetings by intergovernmental organizations for the knowledge sharing benefits it produces.

I am here in Accra on invitation of WHO-CC attending a conference. If I get copies of these presentations, we will use them to work better when we go back to my country. (Participant 3)

MSH Country groupings: All three groups discussed the same social resources such as building better relationships with partners, ensuring efficient collaborations and linkages with other national centres. For example, the national centre in Cape Verde (group 1) has taken the lead to get all Portuguese speaking countries in Africa to form a partnership for resource mobilization. As of November 2015, Mozambique (group 2) and Angola (group 1) were on board according to the interviews. Another example is Kenya (group 2) and Rwanda (group 1) who are members of the East African Community harmonization for resource sharing. Countries in groups 1 and 2 appear to hinge their operations on what resources partners can provide.

We don't have funds from the Ministry, sometimes we get support from Global Fund or MSH and it's not fixed so we are not sure how to plan. (Participant 1)

While countries in group 4 did not specifically discuss social resources, they appear to have been able to build long term trust-based relationships with some organizations:

MSH is still giving us technical support for active surveillance as we requested from them but not for routine activities. (Participant 12)

DISCUSSION

This paper examined the organizational capacity elements (resources and relationships) that strategic leaders in national centres in Africa typically associate with successful and unsuccessful experiences in order to provide insight into the types of resources and relationships national centres need in order to deliver on their mandate. A key finding is that national centres in Africa appear not to be the central coordinating bodies of PV in their various countries but rather conduct a large part of their activities in project-like settings in close collaboration with public health programmes, development partners, intergovernmental organizations and academia. Moreover, national centres experience difficulties in acquiring different types of resources, particularly from national governments, which has made them reliant on external stakeholders, particularly development partners. The difficulties appear to restrict the abilities of national centres to undertake post-market surveillance of the safety and quality of products marketed in the country and the ability to generate the necessary data for evidence-based decision making.

Resource deficiencies have been previously cited as a barrier to the successful delivery of national centres' mandate (6), (9), (10), (21), (23). In a publication in the WHO's World Medicines Situation series, Pal et al (8) showed that most national centres in developing countries were severely understaffed and under-resourced with their PV agenda being very much donor-driven. Subsequently, a 2012 assessment of 9 African countries by the USAID-SIAPS programme revealed that regulatory infrastructure for PV is weak with only 41% having a PV national policy, 30% with legislations for ICSR reporting, 28 % having legal provisions that required MAHs to report ICSRs and only 17% requiring MAHs to conduct post-marketing surveillance activities. These publications showed that national centres in developing countries have limited organizational capacity. A recent review of pharmacovigilance in resource limited countries (10) showed that national centres are still characterized by a lack of capacity to collect data. A study by Ampadu et al (24) on the features of national centres in Africa showed that with the low numbers of ICSRs reported to VigiBase®® most national centres have insufficient data to provide locally-relevant evidence on the benefits and risks of medicinal products.

Our study goes beyond these studies to distinguish between the various resource elements that centres need to deliver and by associating these resource elements with relevant stakeholders in the PV system. This enables a more nuanced examination of the fundamental requirements for sustainable PV in Africa and the organizational capacity needed by African national centres to deliver on their mandate. Our findings are generalizable in terms of geographic context, language, MSH country groupings and year of joining PIDM (Table 3). There is a bit of over-representation of relatively recently established national centres in group 1-2 systems. Our sampling strategy and the resulting findings are thus particularly pertinent for relatively new centres in the systems with limited capacity for PV.

Based on our study, we found 3 core challenges that affect the organizational performance of national centres in Africa.

The first challenge is over-reliance on development partners. Pharmacovigilance in most countries started and/or have been facilitated by technical and financial support from development partners, usually the Global Fund, MSH through USAID or the Bill and Melinda Gates Foundation. This has led to a situation whereby national centres align their planning activities with those of the funding partners. Whilst this has been useful in several cases, it has also left national centres vulnerable. Changes of priorities by the development partners have often led to near-cessation of PV activities. Countries are also unable to undertake long-term planning due to uncertainties and volatility of financial support from partners.

The second challenge is the seeming indifference of national governments to provide support after national centres have gained membership of the PIDM. National governments tend to provide some political and modest technical support by designating national centres and launching them publicly. Occasionally, national

Table 3. National pharmacovigilance centres in Africa (Full PIDM members) (6, 13)

Country	National regulatory authority/National PV centre	Year of joining the PIDM	Included in this study	MSH country group
Angola	Direcao Nacional de Medicamentos e Equipmentos	2013	✓	Group 1
Benin	Direction de la Pharmacie et des explorations diagnostics	2011		
Burkina Faso	Direction Générale de la Pharmacie, du Médicament et des Laboratoires	2010		
Cameroon	Direction de la Pharmacie, du Médicament et des Laboratoires	2010	✓	
Cape Verde	Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares	2012	✓	
Eritrea	National Medicine and Food Administration	2012	✓	
Liberia	Liberia Medicines and Health Products Regulatory Authority	2013	✓	
Madagascar	Direction de la Phamacie, des Laboratoires et de la Médecine Traditionnelle	2009		
Mauritius	Pharmacy Board, Ministry of Health and Quality of Life	2014	✓	
Niger	Direction de la Pharmacie, des Laboratoires et de la Pharmacopée Traditionnelle	2012	✓	
Sudan	National Medicines and Poisons Board	2009		
Swaziland	Pharmaceutical Services Department	2015		
Botswana	Drug Regulatory Services, Ministry of Health and Wellness	2009		Group 2
Congo, Democratic Republic	Direction de la Pharmacie et du Médicament.	2010	✓	
Côte d'Ivoire	Direction de la Pharmacie et du Médicament.	2010		
Ethiopia	Food, Medicine and Health Care Administration and Control of Ethiopia	2008	✓	
Guinea	Direction Nationale de la Pharmacie et du Laboratoire	2013		
Kenya	Pharmacy and Poisons Board	2010	✓	
Mali	Direction de la Pharmacie et des Médicaments	2011		
Mozambique	Departamento Farmacêutico	2005	✓	

Table 3. (continued)

Country	National regulatory authority/National PV centre	Year of joining the PIDM	Included in this study	MSH country group
Rwanda	Department of Pharmaceutical Services	2013	✓	Group 2
Senegal	Direction de la Pharmacie et du Médicament	2009	✓	
Sierra Leone	Pharmacy Board of Sierra Leone	2008	✓	
Togo	Direction des Pharmacies, des Laboratoires et des Equipements Technique	2008		
Zambia	Zambia Medicines Regulatory Agency	2010		
Zimbabwe	Medicines Control Agency Zimbabwe	1998	✓	
Ghana	Food and Drugs Authority	2001		Group 3
Tanzania, United Republic	Tanzania Food and Drugs Authority	1993		
Namibia	Namibia Medicines Regulatory Council	2009	✓	Group 4
Nigeria	National Agency for Food and Drug Administration and Control	2005	✓	
South Africa	Medicines Control Council	1992		
Uganda	National Drugs Authority	2008		
Egypt	Egyptian Drug Authority	2002		N/A
Morocco	Direction du Me´dicament et de la Pharmacie	1992		N/A
Tunisia	Direction de la Pharmacie et du Médicament	1993		N/A

governments have passed subsidiary legislation to help the work of the national centre. However, in several cases this support seems to evaporate once countries become members of the PIDM leaving national centres bereft of resources. This is reflected in the data published by Ampadu et al (24) where most national centres in Africa appear to do the barest minimum to gain membership of the PIDM by sending 20 ICSRs to VigiBase®. Thereafter, national centres activities seem to slow down spectacularly with few exceptions. In view of the important role expected by national centres of their governments, it is important for the national centre and other stakeholders to continue advocating to these national governments for long-term resources for their national centres in order to fulfil their expected role of providing the needed safety surveillance infrastructure in their countries.

The third core challenge facing national centres is how to engage all PHPs in a sustainable way. The interview data showed that in nearly all countries, national centres are successful in engaging some but not all PHPs. Establishing trust-based relationships with PHPs require adequate human and technical resources most of which are limited in national centres. Public health programmes are the main providers of data for national centres in Africa (24), (25) hence successful collaboration with them will provide not just the needed data but also associated resources. It is however, difficult to see how this can be done sustainably if national centres rely on these programmes for their resources. Collaboration between national centres and PHPs is accepted as extremely important and beneficial to both organizations and the WHO strongly encourages this as stated in the WHO manual "Pharmacovigilance in Public Health Programmes" (26). To encourage efficient collaboration with PHPs it would be important to research and provide guidance on the factors underlying successful collaboration between national centres and individual PHPs.

The fight against counterfeit medicines was not mentioned in any of the described experiences. This is surprising given that it is a known and ongoing problem in low and middle-income countries (27), (28). In an article by WHO, it was estimated that one in 10 medicines in low-income countries are counterfeit and likely responsible for the deaths of tens of thousands of children from diseases such as malaria and pneumonia every year (29). Several researchers have concluded that to combat this problem regulators will need sustained political will, financial support, tools and technical capacity to enforce quality standards in manufacturing, supply and distribution and a coordinated action from the police, customs officials, and Marketing Authorization Holders (30). National centres could play a role in this but our analysis did not reveal activities focused on counterfeit medicines as a key priority. To address this problem an effective PV programme with enforcement power is needed. Further, it is also surprising that in only a limited number of experiences industry and academia were mentioned as stakeholders. One of the reasons for this might be that there is little industry and academic activity as pertains to pharmacovigilance in the systems under study.

We provide a number of recommendations based on our findings and discussions. First, to further strengthen and expand PV systems in sub-Saharan Africa it is important to develop approaches that allow for sustainable financial and technical resources for national centres as these resources have been identified by strategic leaders as key impediments to the functioning of national centres. National governments will remain the key expected provider of these resources; however, innovative approaches involving collaboration between development partners, public health programmes, academia and industry could be explored as has also been suggested by Pirmohammed et al. (21). Such collaborative approaches might also help in preventing a situation where national centres become overly dependent on a single stakeholder. Second, it is important that international organizations like WHO and the Global Fund earmark a certain percentage of funds for medicines and vaccines to be set aside solely for safety surveillance and the maintenance of the safety surveillance and quality infrastructure. Third, mandatory QPPV programmes as required in Ghana and other legally enforceable instruments put responsibility on surveillance and the provision of safety data on the pharmaceutical industry who should be a main provider of safety data to national centres (31). Finally, academic and research institutions could go beyond incorporating PV in their curricula to embarking on PV research and developing tools and techniques relevant for safety surveillance in their respective national context. They could do this in collaboration with national centres. This will contribute to the development of innovative and pragmatic pharmacovigilance approaches (32) that are highly needed for SSA countries.

Conclusions

This study concludes that national centres in Africa are faced with 3 core challenges. The first is over-reliance on development partners. The second challenge is the seeming indifference of national governments to provide support after national centres have gained membership of the WHO Programme for International Drug Monitoring (PIDM) and the last core challenge facing national centres in Africa is how to engage all public health programmes in a sustainable way.

ABBREVIATIONS

PV: Pharmacovigilance; ADR: Adverse Drug reaction; WHO: World Health Organization; MAH: Market Authorization Holder; RCORE: Regional Centre of Regulatory Excellence; AMRH: African Medicines Regulatory Harmonization programme; MSH: Management Sciences for Health; IPAT: Indicator-based Pharmacovigilance Assessment Tool; JSI: John Snow Incorporated; USP: United States Pharmacopeia; USAID: US Agency for International Development; ICSR: Individual Case Safety Reports; DTC: Drug Therapeutic Committee; PIDM: WHO Programme for International Drug Monitoring.

FDA: Food and drug Authority; HCF: Health Care Facility; HCW: Health Care Worker; KNUST: Kwame Nkrumah University of Science and Technology; MoH: Ministry of Health; PRS: Patient Reporting System; SPSS: Statistical Package for the Social Sciences; SSA: Sub-Saharan Africa;

DECLARATIONS

Ethics approval and consent to participate

Per Page 43, Appendix B, Number 2 of the Ghana Health Service Ethics Review Committee's Standard Operating Procedure, ethical review is not needed for a research that uses interviews to document "public behaviour" of professionals working in a public organization and not of patients. All quotes were anonymised to prevent statements being traced back to individuals.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analysed during the current study are available from the corresponding author on request.

COMPETING INTERESTS

All authors declare that they have no competing interests.

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No external sources of funding were used for the conduct of this study, or for the writing, correction, and submission of this article.

AUTHORS' CONTRIBUTIONS

HHA and JH conceived and designed the study. HHA conducted the data collection and analysis. DA and MAD helped with the transcription and data analysis. JH and ANOD supervised the study. HHA, JH, ANOD and HGML contributed to interpretation of the results and writing of the manuscript. All authors approved the final version of the manuscript.

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APPENDIX A: INTERVIEW QUESTIONNAIRE

Strategic Leaders in National centres in Africa Interview Protocol

Topic: Successful and Unsuccessful Pharmacovigilance experiences in Africa

Introductory Protocol

This interview will be in the form of an audio-taped face to face conversation. For your information, only researchers on this project will be privy to the tapes; which will be destroyed after they are transcribed. All information will be held confidential. The interview is about 20 minutes.

Introduction

I have requested to interview you today because I know you have been active in the field of pharmacovigilance for several years. This study focuses on successful and unsuccessful pharmacovigilance experiences in Africa. The research does not aim to evaluate your techniques or experiences, nor will the information be used as a tool to penalize you.

Participant (Name, Title, Position and Country): _____

Interviewer (Name and Title): _____

Interview Questions

1. Describe 3 situations where PV was successful in your country?
   - Why was PV successful?
   - Could this experience be replicated in another African country or is it country specific?

2. Describe 3 situations where PV was unsuccessful in your country?
   - Why was this activity particularly not successful?
   - Could this experience be replicated in another African country or is it country specific?

3. Is there anything else you will like to discuss with me?

CHAPTER 3

PARTICIPATION AND AWARENESS OF REPORTERS AND EVALUATORS

CHAPTER 3.1

THE CONTRIBUTION OF GHANAIAN PATIENTS TO THE REPORTING OF ADVERSE DRUG REACTIONS: A QUANTITATIVE AND QUALITATIVE STUDY

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ABSTRACT

Background

Under-reporting of Adverse Drug Reactions (ADRs) is a major challenge for pharmacovigilance in Africa. This study sets out to assess the level of awareness of Ghanaian patients about ADRs and ADR-reporting and explores how different patients in Ghana recognize an ADR and the steps they take when they experience an ADR.

Methods

This was a two-part study consisting of a survey to quantify the awareness of Ghanaian patients on ADRs and ADR-reporting, and in-depth interviews to explore how patients recognize an ADR and the steps they take thereafter. Participants were selected from 28 health care facilities (HCF) in rural and urban areas in 4 out of the 10 administrative regions of Ghana. Chi-squared tests were used to examine associations between demographic variables and i) awareness of ADRs and ADR-reporting, ii) ADR experience and iii) awareness of the Ghana Food and Drug Authority (Ghana-FDA) and its patient reporting system (PRS). Only participants that indicated they experienced an ADR were included for the in-depth interviews. Data was investigated for participants' awareness of ADRs, ADR reporting and steps taken when they experience ADRs.

Results

Of the total 572 participants enrolled in the study, 14% indicated they were unaware of ADRs and were excluded. Of the remaining 491 participants, 38% had experienced an ADR, of which 67% reported the ADR, 68% of them reported it to a doctor. Only 3% of the 491 participants were aware of the Ghana-FDA's PRS. The interview phase consisted of 33 patients who had experienced an ADR. Three key findings from the interview phase were; most participants recognized an ADR themselves, the symptoms of the ADR were the most mentioned reason for reporting and participants experienced a wide variety of obstacles in ADR-reporting.

Conclusions

Most Ghanaian patients appear unaware of or unable/unwilling to use formal national channels for ADR reporting like the Ghana-FDA PRS. Motivation for ADR reporting appeared mainly personal and not communal. These findings warrant further attention in order to increase patient reporting of ADRs.

Keywords

Pharmacovigilance, Patient reporting, Adverse Drug Reactions, Communication, Questionnaire, Patient interviews

INTRODUCTION

Spontaneous reporting of Adverse Drug Reactions (ADRs) is the cornerstone of pharmacovigilance. ADRs continue to be a major public health issue as they are a major cause of patient morbidity and mortality (1). The costs associated with treatment of ADRs are an economic burden on resource-limited health care systems such as those in most African countries (2).

An important aim of pharmacovigilance is the detection of signals by timely sharing of data on ADRs to identify previously unknown medicines-related safety issues. Per the World Health Organisation's (WHO) definition, an ADR is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (3). Worldwide, under-reporting of ADRs is a major challenge for successful pharmacovigilance (4). Under-reporting is particularly problematic in Africa and is well documented (5-8). Individual case safety reports (ICSRs) from Africa to the WHO International Database - VigiBase™ is less than1% of the global total even though Africa has 15% of the world's population (5). Several studies have been carried out to explore the high under-reporting in Africa compared to other regions. Most of these studies focus on under-reporting by health care workers (HCWs) (9-11).

To address the issue of under-reporting, some countries in Africa, e.g. Ghana and Kenya, have embarked on patient reporting initiatives (12-13). Patient reporting is generally seen as a positive development for pharmacovigilance (14). In the Netherlands, for example, patient reporting has been shown to increase the number of reported ADRs and also provides a new perspective on the experiences of ADRs (15). Whilst data from the Netherlands and other high-income countries cannot necessarily be translated to Africa, it is encouraging to notice the efforts made by national pharmacovigilance centres in Africa to promote direct patient reporting as a means of overcoming chronic under-reporting. For patient reporting to work however, it is important for patients to be aware of ADRs and the formal national channels for reporting ADRs and to be able to recognize an ADR. They must be able to easily use these channels and should find value in using them. There is paucity of data on patients' awareness of ADRs in Africa and even more limited data on direct patient reporting of ADRs in Africa. There is also little understanding of how patients identify ADRs and what they do when they experience an ADR.

Adverse drug reaction reporting awareness campaigns in sub-Saharan Africa (SSA) countries typically focus on HCWs and rarely on patients. However, it is patients who experience ADRs and are able to give a first-hand account of what they have experienced making them an integral part of any ADR reporting process (16). A study in the Netherlands concluded that the severity of the ADR and the need to share experiences were the main reasons why patients reported ADRs (17). Research in Portugal showed that patients were more likely to spontaneously report ADRs which

are severe or when they were worried about the symptoms of the ADR (18). These findings, however, cannot be wholly extrapolated to SSA because of major differences in health care delivery systems, accessibility of HCWs, awareness of ADRs and health care regulations (7). Moreover, there are differences in levels of education, culture and living conditions amongst people in Ghana and other SSA countries compared to those living in Europe and other high-income countries. Such differences may lead to variations in knowledge and perception on medications, ADRs and ADR reporting (19, 20). It is also of importance to know what motivates patients in Ghana to report an ADR and whether they know the formal channels for ADR reporting including direct patient reporting. A recent study by Sabblah et al. on patients' perspectives on ADR reporting in Ghana concluded that there is high patient awareness (82%) of the national pharmacovigilance centre and relatively high ability to report (50%) (21). The work by Sabblah et al., however, took place in only 2 pharmacies (out of the national total >15,000 pharmacies and other licensed dispensers of medicines) and consisted of investigator-administered structured questionnaires. This limits the generalisability of the findings towards the whole country, but it shows the importance that researchers are attaching to patient reporting of ADRs. We therefore set out to find the potential contribution of Ghanaian patients to the ADR reporting process by identifying the quantum of reporting by patients and their awareness of the various channels for direct patient reporting of ADRs. To build upon the work of Sabblah et al., our study involved 28 facilities in 4 administrative regions of Ghana including rural and urban areas to ensure stronger external validity. Our study aimed to quantify the awareness of Ghanaian patients on ADRs and ADR reporting and explore how patients in Ghana recognize an ADR and the steps they take after experiencing an ADR by using mixed methods.

METHODS

This is a two-part study involving both quantitative and qualitative approaches. The first part consisted of a survey to quantify the awareness of Ghanaian patients on ADRs and ADR-reporting. The second, qualitative part consisted of one-on-one in-depth interviews to explore how Ghanaian patients recognize an ADR and the steps they take when they experience an ADR.

Selection of participants

Participants were selected from 28 health care facilities (HCF) in rural and urban areas in 4 out of 10 administrative regions of Ghana (Ashanti, Greater Accra, Eastern and Central regions). The HCF included government hospital pharmacies, private hospital pharmacies, community pharmacies and licensed Over The Counter (OTC) medicine sellers also known as "chemical sellers" to cover the full Ghanaian drug delivery system. Participants reflected multiple local language groups and were randomly

selected after being supplied medication at a pharmacy or dispensary. They had to be at least 18 years and speak English, Twi, Ga or Fante. The researchers aimed to include an average of 20 participants per HCF to have an indicative sample of the population from the different facilities. So, the total targeted sample size was 560 participants.

Participants who indicated they had experienced an ADR in the survey phase were eligible for enrolment into the interview phase. Participants were selected by means of the maximum variation sampling strategy in order to obtain data from a wide range of patients (22). The factors considered in the sampling strategy included gender, age, educational attainment, severity of experienced ADRs, whether or not the ADR was reported and rural/urban area of living. Data analysis started after conducting 20 interviews and the selection process continued until no new themes or categories emerged from the final four interviews (data saturation).

Data collection and analysis

All surveys and in-depth interviews were conducted between November 2016 and December 2016.

Survey

In addition to the collection of demographic information, our survey included 7 questions and 5 sub-questions about the participants' awareness of ADRs, their reporting behaviours and the information provided by the pharmacy or dispensary on possible ADRs to the dispensed medicines [see Additional file 1]. Two trained research assistants and the lead investigator (TJ) conducted all surveys. Upon being dispensed a medication at the pharmacy or dispensary, the researchers approached the potential participant. The rational of the study was explained, verbal informed consent sought and if participant agreed, they were enrolled into the study. The survey was piloted twice, respectively on 3 and 10 participants with different demographics. The pilots led to some changes in the formulation of the questions. The data from the pilots were not included in the analysis.

Chi-square tests were used to compare the demographic variables and i) awareness of ADRs and ADR-reporting, ii) whether participants had experienced ADRs and iii) awareness of participants on the Ghana Food and Drug Authority (Ghana-FDA) and its patient reporting system (PRS). Additionally, the Mantel-Haenszel test for trend was performed to check for differences in awareness of ADRs and ADR reporting in groups of patients with different age ranges and educational levels. Statistical Package for the Social Sciences (SPSS) software version 24 was used for all statistical analyses.

In-depth interviews

A concise guideline was developed for the in-depth interviews. The guideline consisted of an introduction and 7 main questions on the four themes in the Conceptual Framework below (figure 1).

The way patients discover ADRs (Discovery) and reasons why they act when experiencing an ADR (Action) were two themes within the conceptual framework based on earlier studies (17, 18, 22, 23). These earlier studies focussed on the themes separately, mostly with a quantitative methodology and in high-income countries. Our study used a qualitative methodology to provide a better understanding of all the steps patients take when they experience ADRs. Awareness of ADRs (Awareness) was a theme deduced from the surveys. Most sub-themes as well as the fourth theme about the outcome of reporting an ADR (Outcome) emerged inductively from the interview data. This theme included expectations of the patient about further actions taken by the HCW with the report of the ADR and the result of the consult with the HCW. The interview guideline underwent some minor changes after the first 4 interviews and reflects these four themes and their subthemes [see Additional file 2].

The interviews took place at the participant's home or place of work to make them feel more comfortable and free to speak. Prior to the interview, written consent was sought. The consent form was read to participants with low literacy and they signed with a thumbprint. The lead investigator conducted all in-depth interviews in the presence of a translator. The interviewer asked follow-up questions if necessary for clarification.

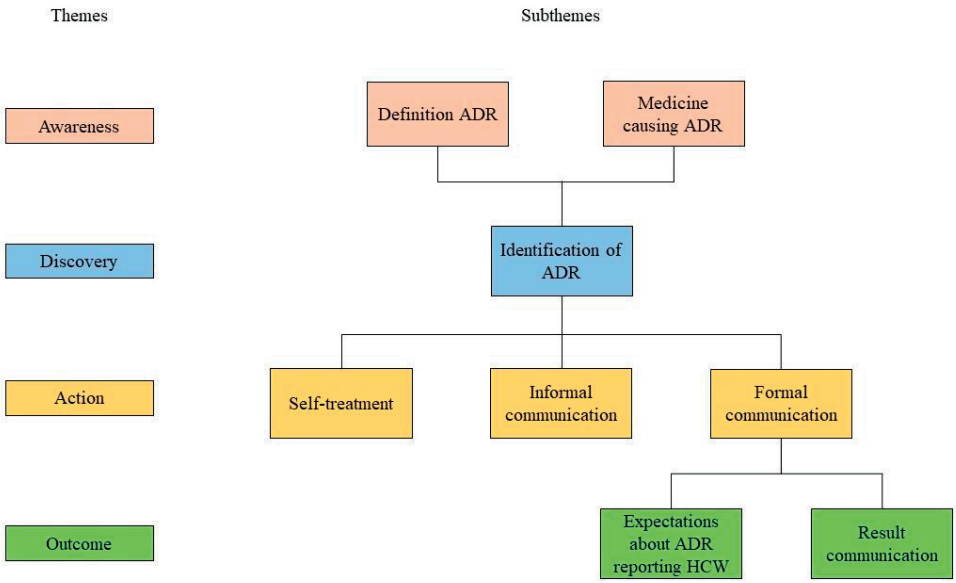

Figure 1. Conceptual framework used in the qualitative data analysis
Adr = Adverse Drug Reaction, Hcw = Health Care Worker

Each interview ended with the interviewer providing the participant the opportunity to speak freely about the issues discussed. Each participant was interviewed once with the interviews ranging between 10-20 minutes. All interviews were electronically recorded and transcribed verbatim by the lead investigator. Two research assistants assisted in transcribing the interviews conducted in local languages.

Data analysis of the interviews was conducted by the qualitative content analysis process using the themes awareness, discovery, action and outcome as outlined by Bengtsson (24) and Elo and Kyngas (25). The analysis was both a deductive and inductive process in that the data was investigated for *a priori* issues relating to the objective but also captured unanticipated explanations and patterns. The inductive approach was particularly important to identify new actions and reasons to act after experiencing an ADR. Awareness, action and discovery were used as preformulated leading themes. Initial reading of 20 randomly selected transcripts was done by the lead investigator, units of meaning of the themes in sentences or paragraphs were highlighted and explanations of why it was important were noted. The highlighted units of meaning were then abbreviated in codes. These codes were grouped into categories within subthemes of the conceptual framework (figure 1) or new subthemes that emerged. A more experienced research team member (HHA) also coded the 20 randomly selected transcripts and both sets of codes were compared. The process of rereading transcripts and updating the framework continued until no further modifications were needed. This updated framework was used for the second coding process. In this process, 10 interviews were read and coded by four research team members together at the same time. The remaining 23 transcripts were read and coded by the researchers individually and discussed afterwards. All codes were substantiated with quotes and explanations, which were used to identify and interpret patterns in the data. The NVivo software program (version 11) was used to assist the analysis.

Ethical approval

The research protocol was reviewed and approved by the Committee on Human Research, Publications and Ethics of the Kwame Nkrumah University of Science and Technology (KNUST), reference number: CHRPE/AP/481/16.

Survey results

A total of 572 participants were enrolled in the study. However only 571 surveys were analysed because one survey was completed incorrectly. The demographic characteristics of the participants are shown in Table 1.

In this study, 14% of participants (n=80) indicated they had never heard of the words "side effect", "adverse drug reaction" or their local equivalents. These participants were excluded from answering any further questions in the survey. Of the remaining

Table 1. Demographics of all participants from the survey and the in-depth interviews compared to the numbers population of Ghana from 2010 (26)

	Survey		In-depth interviews		Figures Ghana
Variable	N	%	N	%	%
Gender					
Female	293	51.3%	13	42.0%	52.8%
Male	278	48.7%	18	58.0%	47.2%
Age					
18-24	70	12.3%	1	3.0%	24.7%*
25-34	127	22.2%	8	26.0%	27.3%
35-44	117	20.5%	6	19.0%	19.1%
45-54	108	18.9%	7	23.0%	13.0%
55-64	76	13.3%	6	19.0%	7.3%
65-74	54	9.5%	3	10.0%	4.7%
75 ≤	19	3.3%	0	0.0%	3.8%
Education**					
None	56	9.8%	3	10.0%	28.5%
Primary/JSS/JHS	191	33.5%	8	26.0%	341.%
Secondary/SHS/SSS	173	30.3%	10	32.0%	27.3%
Tertiary	149	26.1%	10	32.0%	10.2%
Unknown	2	0.3%	-	-	-
Area of living					
Rural area	140	24.5%	8	26.0%	49.1%
Urban area	431	75.5%	23	74.0%	50.9%

JSS = Junior Secondary School, JHS = Junior High School, SSS = Senior Secondary School, SHS = Senior High School * age group 15-19 was used, corrected to age range 18-19 and added to age group 20-24. **The figures from the educational attainment in Ghana and the four regions are from people 15≤ years old.

491 participants who completed the survey, majority were aware of ADRs and that it was possible to report these ADRs. However, examination of the data indicated that there was limited awareness of the formal ADR reporting system in Ghana as shown in Table 2. Only 45 of the 491 participants had heard of the PRS and of these only 16 (36%) indicated they knew how to report an ADR via the PRS, meaning only 3% of the total population that finished the survey knew how to report an ADR using the PRS. Moreover, only 0.5% of all participants who knew where to report, indicated they would report directly to the Ghana FDA, while 68% of them would report to a doctor. Of 439 participants that received medicines from the dispensary, 6% received information about possible side effects of medicines from their HCW. Participants with higher education were significantly more likely to be familiar with the words "side effect", "ADR" or their local translation ($p<0.001$). Additionally, they were more likely to be familiar with the organisation that is responsible for ADR reporting (Ghana FDA) and the PRS ($p<0.001$). Participants with a higher education level also experienced an ADR more frequently ($p<0.001$). Older participants were significantly

Table 2. Persons or institutions to whom the participants reported or would report an adverse drug reaction (ADR)

	Responses		Gender	Age	Education	Area of living
Are you familiar with the word side effect or ADR?	Yes	491 *(86.0%)*	p = 0.329	p = 0.004*	p = <0.001*	p = 0.038*
N = 571	No	80 *(14.0%)*		T = 0.014*	T = <0.001*	
Did you ever experience an ADR?	Yes	186 *(37.9%)*	p = 0.849	p = 0.018*	p = <0.001*	p = 0.084
N = 491	No	305 *(62.1%)*		T = 0.624	T = <0.001*	
Did you report the ADR?	Yes	123 *(67.2%)*	p = 0.963	p = 0.451	p = 0.424	p = 0.322
N = 186	No	60 *(32.8%)*		T = 0.066	T = 0.475	
Do you know where to report?	Yes	425 *(86.6%)*	p = 0.913	p = 0.817	p = 0.097	p = 0.231
N = 491	No	66 *(13.4%)*		T = 0.891	T = 0.033	
Do you know the organisation responsible for collecting reports of ADRs?	Yes	33 *(6.7%)*	p = 0.664	p = 0.704	p = <0.001*	p = 0.017*
N = 491	No	458 *(93.7%)*		T = 0.527	T = <0.001*	
Are you familiar with the PRS?	Yes	45 *(9.2%)*	p = 0.162	p = 0.238	p = <0.001*	p = 0.047*
N = 491	No	446 *(90.8%)*		T = 0.159	T = <0.001*	
Information about ADRs provided by pharmacists	Yes	25 (5.7%)				
N = 439	No	414 (94.3%)				

FDA = Ghana Food and Drug Authority, MoH = Ministry of Health.
* indicates statistical significance.

more likely to be familiar with the words "side effect", "ADR" or their local translation (p=0.004) compared to younger participants. Similarly, participants living in urban areas were more likely to be familiar with these words (p=0.038) than participants living in rural areas. They were also more likely to be familiar with the organisation that is responsible for ADR reporting (p=0.017) and the PRS (p=0.047).

3.1 IN-DEPTH INTERVIEW RESULTS

In total, 33 participants were enrolled in the interviews (Table 1). Two interviews were excluded from the analysis leaving only 31; one participant did not understand the questions and could not answer them, and a second participant had a very different explanation of an ADR.

Awareness

Participants were asked to define an ADR in their own words. Most participants (n=21) described an ADR as a negative reaction after taking a medicine. Other participants mentioned every effect after taking a medicine (n=4), an unexpected effect after taking a medicine (n=3), the effect after taking an overdose of a medicine (n=2) or the medicine is not working (n=1) as definitions of an ADR. For example, one participant described an ADR as: *"If you should take the drug and should become plenty, it gives you a side effect."* [Participant 7: male, finished primary school]. Secondly, patients were asked if they knew the name of the medicine that caused the ADR. Half of the participants did not know the name of the medicine; most of them mentioned that they forgot (n=4) or just didn't know the name of the medicine (n=9). Two participants indicated they did not know the medicine that caused the ADR, because they took multiple drugs: *"If I was taking one particular medicine, I would say 'okay when I take this medicine, this is the side effect'. But when you are taking combined drugs, taking about 4-5 different types of drugs, you cannot tell. There is no way you can tell."* [Participant 26: male, finished tertiary education]

Discovery

Patients were asked how they knew they were experiencing an ADR. Most participants (n=26) assessed the ADR themselves. They could relate the medicine to the symptoms they were experiencing without the help of a second person. Most of them related the ADR in time fashion (or temporally) with a certain medicine (n=23). Also, some participants read the patient information leaflet or did research on the internet. The temporal assessment of an ADR is illustrated by a quote: *"The way I was before I visited the hospital, it has become over (after taking the medicine)."* [Participant 11: female, no education]

Only one participant assessed an ADR with the help of a family member. The remaining 4 participants had their ADRs assessed by a HCW; a doctor because

they thought the ADRs were a disease: *"The person (general practitioner) checked my folder (hospital dossier) and realized that the drug I was given, gave me the reaction."* [Participant 4: female, finished secondary education]

Action

In-line with this theme, the researchers first asked what the patient did when they experienced an ADR and what motivated them to do something about it. Most of them took multiple actions after experiencing the ADR. Based on the data, three main possible actions were deduced: self-treatment, informal communication and formal communication.

For self-treatment, most participants (n=14) stopped taking the medicine without or before consulting someone. One participant mentioned he reduced the dose of the medicine, one started taking other medicines for the ADR and three tried to minimize the symptoms of the ADR. An example: *"Water is good, so I take water, always taking more water so that the thing (the ADR) can come out. So that is what I did."* [Participant 25: female, finished secondary education]. The other participants (n=11) did not self-treat. We defined "informal communication" as communication with other patients, family members or friends. Most participants mentioned they discussed the ADR with family members (n=21) and friends (n=9). Some participants were advised by a relative or friend to visit a HCW or to be careful with the medication. Others instructed and educated family members or friends about the ADR. They often advised them not to take that same medicine (n=8). For example, one participant said *"when I see somebody I say: be careful when you take that drug. That, I think, is the best I could do."* [Participant 17, male, finished tertiary education]. Another action that could be distinguished within informal communication was the communication with fellow sufferers who experienced the same ADR (n=5). They mainly advised each other not to buy or take the medicine in question again. Finally, some participants had no informal communication (n=3) and in two of the interviews, the participants did not mention having informal communication.

The third action, formal communication, included participants that reported their ADR through formal channels. None of the participants had reported an ADR to the PRS. They reported their ADRs to a doctor (n=19), a pharmacist (n=3), a medical inspector (n=1) or a nurse (n=1). They reported to a specific HCW because they prescribed the medicine that caused the ADR. Participants also mentioned they visited a doctor rather than a pharmacy, because they have more faith in the knowledge of the doctor. For example, a participant who visited the doctor mentioned: *"Because they (doctors) have a lot of information."* [Participant 10: female, finished tertiary education]. One participant mentioned that she went to a specific doctor, because her health insurance only covered for that doctor. One participant went to a doctor because her mother worked at that HCF as a nurse, and she did not want to report the ADR out of shame.

When an ADR was reported, the patients were asked why they reported it. Participants mentioned multiple motives to report an ADR. However, none of them described communal motivations such as contributing data to the reporting system or the knowledge based on ADRs. Most participants (n=16) reported because of the symptoms they were experiencing. Those participants either wanted to treat the symptoms of the ADR, thought their symptoms were caused by another disease or the initial disease was not cured yet. Other participants were seeking for more information about the ADR (n=4). These motives are driven by the wellbeing of the participant itself. Other participants were advised by other people to visit a HCW (n=4), wanted to complain about the medicine (n=4) or wanted to complain about the HCW who prescribed the medicine (n=2). An example: *"I went there (the pharmacy) with an expectation, because I want her (the head pharmacist) to know that some of the people she is working with are not competent or don't know their work. For that matter, that is going to bring a lot of effects on us."* [Participant 9: male, finished primary education]. One participant mentioned that she was taught that she had to see a HCW every time she experienced an ADR. She said: *"So if we take a medicine and it is not good, we must come back here (the hospital)."* [Participant 11: female, no education]. These motives were focussed mainly on personal benefit.

According to the interviews 7 participants did not have any formal communication, some of them were not aware they could visit a HCW with an ADR, others doubted the capability of the HCW, did not want to bother the HCW or thought the distance to the health care facility was too far. Some participants also did not want to visit the HCW because the self-treatment was successful already or the medicine that caused the ADR was not prescribed or bought from a pharmacy in a health care facility. An example: *"Oh, because I didn't buy the medicine from them (pharmacy/hospital) so I can't go and report there."* [Participant 13: male, finished tertiary education].

Outcome

If a patient reported an ADR through a formal channel, they were asked about the outcome of their reporting. Some of the outcomes from formal communication were; the HCW changed the medicine that caused the ADR (n=17), gave an additional prescription (n=4) or did nothing (n=4). In the 19 interviews where participants' expectations on ADR-reporting or follow-up were discussed when talking about outcomes, only one participant thought the HCW wrote down the ADR in his medical folder. The other participants were not certain what the HCW did with their report (n=9), mostly because the HCW did not communicate with them. For example, one participant said: *"Because at times if they (doctors) give you some drugs, you take it and then you feel something (ADR). Next time when you go there and tell them, they just hear you, but they will not say anything."* [Participant 32: female, finished primary school]. The remaining participants thought the doctor did not do anything (n=9) with

their report. One participant said: *"You go to a doctor (to report an ADR), he takes his money and end of story."* [Participant 20: male, finished secondary school].

DISCUSSION

This study aimed to quantify the awareness of Ghanaian patients on ADRs and ADR-reporting and to explore how patients recognize an ADR and the steps they take thereafter. A key finding from the survey was that of the 491 participants, 38% had experienced an ADR of which 67% reported the ADR. Of these 68% reported it to a doctor. Overall, only 3% were aware of the Ghana-FDA's PRS. Participants with higher education were more likely to have experienced an ADR whereas participants with higher education or living in urban areas or both were significantly more likely to be aware of ADRs and the PRS. Three key findings from the interview phase were that most participants recognized an ADR themselves, the symptoms of the ADR were the most mentioned reason for reporting and participants experienced a wide variety of obstacles in ADR-reporting.

The results from our survey differ considerably from that published by Sabblah *et al*. who found high patient awareness (82%) of the National Pharmacovigilance Centre and relatively high awareness of the possibility to report directly to the centre (50%) (21). The different outcomes could be attributed to study design as well as the immediate effect of an FDA-Ghana radio and TV campaign to promote ADR-reporting in June 2016 (21). Our data showed that patients with better awareness of ADRs and those who reported ADRs more often had higher education and more frequently lived in an urban area, which is in line with other findings in literature (18). In low and middle-income countries, especially those with growing economies, disparity throughout the country may be higher than in high-income countries (27) and particularly health literacy may differ substantially between regions (28). Spatial patterns of ADR-reporting may reflect this inequality. The observed differences between the two studies therefore highlight the importance of ensuring wide and diverse coverage of facilities when undertaking such studies, although this comes with associated high cost.

The conclusions from the survey were further explained with interviews. The survey revealed that the majority of participants were aware of ADRs and could report these ADRs. However, the interviews revealed some participants who were aware of the ADRs but did not know the name of the medicines that caused the ADR. The name of the medicine is one of the four mandatory fields that must be completed on an ADR-reporting form according to the Council for International Organisations of Medical Sciences (CIOMS) (29). Therefore, not knowing the name of the suspected medicine(s) makes it impossible to report an ADR. It appears that the inability to recall the names of the medicines is linked to the dispensing practices in Ghana, as in other resource-limited countries. In Ghana it is a common practice to dispense from bulk, patients

are typically given medications in a small white envelope most times not labelled as was also observed by our research team. This provides further evidence supporting previous studies which concluded that issues in dispensing medicines in SSA included poor labelling of dispensed medicines from bulk, poor patient counselling, dispensing by non-pharmacists, less qualified personnel and illiteracy as well as presence of products with labels in other languages apart from the official national languages (30). This is supported by the finding that almost no patient indicated to have received any information about ADRs in this study. Follow-up studies could further investigate the dispensing practices with regard to information provision about ADRs.

In discussing motivations for reporting, a large percentage of participants (67%) indicated they reported the ADR. However, the interviews unearthed that the reasons to report an ADR were mostly driven by personal benefits. These reasons differ considerably from patients in high-income countries whose reasons for reporting were mainly driven by communal motives (31). This can be explained by the substandard information provision by HCWs and the fact that most participants were unaware of the PRS. The communal motives of reporting can only be realised when patients get feedback on the effects of patient reporting and are aware of the PRS and its functioning, e.g. through accumulation of ADRs leading to evidence generation on causality. This will help patients appreciate the fact that reporting is not only for their own benefit but also for the benefits of others. Also, the survey data indicated that only few pharmacists in Ghana provided information about ADRs of the medicines administered to patients compared to other countries (32, 33). The authorities and HCWs concerned need to let patients appreciate the reasons why they must report ADRs and the contribution to public health.

The survey and interviews revealed several obstacles to ADR-reporting. In table 3 all identified obstacles are summarized and potential solutions are suggested. Lax regulatory enforcements appear to play a key role in low ADR reporting. It is a well-known fact in Ghana that medicines can be purchased from anywhere such as in buses, open market and from individuals in addition to the regulated licenced premises. It is estimated that 10-20% of all medicines is obtained illegally, but there are no confirmatory data (34). Unlicensed sellers are mainly driven by financial incentives and are typically not properly educated about ADRs (34), thus are unlikely to provide any information on ADRs or how to report them. Purchasing medicines from unlicensed and itinerant sellers makes it difficult for patients to report ADRs because sometimes they are reluctant to mention or cannot trace where or whom they bought their medicines from as the interviews revealed. The second identified obstacle is substandard recognition of ADRs. It appears that participants in the in-depth interviews mostly assessed ADRs themselves which corresponds with other research (21). The process of recognizing and assessing an ADR adequately is difficult and requires a lot of knowledge and can lead to substandard recognition of ADRs (24). The knowledge gap as revealed by this study can contribute to the low rate of lower educated people

that experienced (or recognized) an ADR compared to higher educated people in this study and compared patients in high-income countries (35, 36).

The first line of care for Ghanaian patients is the pharmacist and pharmacists are more likely to report an ADR when they see one compared to doctors (36). Hence it is of major concern to see from both the survey and in-depth interviews in this study that patients will rather report their ADRs to doctors and not pharmacist/ pharmacy attendants. The survey revealed that Ghanaian patients lack awareness of the PRS and moreover lack the willingness to use it which is a major obstacle in ADR reporting. Also, not being aware of the possibility of reporting an ADR to a HCW emerged in the in-depth interviews as a reason not to report. Finally, being afraid to bother the doctor with an ADR was mentioned in one in-depth interview. Others also indicated that the high socio-economic status of the doctor is a challenging factor in the patient-doctor relation.

Based on these findings, we recommend the Ghana Food and Drug Authority to continue their education and awareness creation about ADRs but also target awareness creation to areas outside the capital cities and use medium of communication that

Table 3. Identified obstacles experienced in ADR-reporting by Ghanaian patients and possible solutions to them

Obstacle	Potential solutions
Poor dispensing practices of medicines	Improve the regulation of medicine dispensing practices.
	Urging pharmaceutical companies to produce smaller medicine boxes
	Educate HCWs on good dispensary practices of medicines in their education program and by in-service training.
Substandard recognition of ADRs by patients	HCWs and primary schools should focus on educating (lower educated) patients on ADRs and how to recognize and assess ADRs.
	An easy tool can be developed to assist patients in the recognition and assessment of ADRs.
Skipping the first line of healthcare in reporting ADRs	The authorities concerned need to make patients more aware of avenues to report and particularly urge patients to report ADRs to their first line of care which is the pharmacy attendants and then other HCWs.
	Pharmacists or attendants in turn need to improve their participation in ADR-reporting by improving their patient engagement with the hope of establishing a lasting trust-based relationship.
Lacking awareness to report ADRs to HCWs	Better information provision practices from HCWs by including ADR reporting/patient education in the curriculum of healthcare disciplines
	Targeted campaigns by the Ghana-FDA.
Socio-economic differences between patients and HCWs	Point out alternative options for patient reporting of ADRs such as their first line of care (pharmacist) and/or the PRS.
Lacking awareness of the PRS and willingness to use it	Campaigns to make patients aware of the PRS
	Creating a patient-friendly version of the PRS

citizen's living in these areas are familiar with. Further, it is important not to settle on one dominant route for ADR reporting but keep the system flexible and allow for different ways of reporting depending on patient needs and geographical contexts. We suggest that an emphasis on the benefits of patient reporting and on different routes to facilitate such reporting should form part of all awareness campaigns.

This study is the first of its kind to obtain data on the behaviour of Ghanaian patients when they experience ADR from the patient's perspective using mixed methods. Moreover, the population in both parts of the study was heterogeneous and representing 4 administrative regions of Ghana including the 2 most populous regions – Greater Accra and Ashanti regions. Also, participants in rural areas were included. More highly educated participants, elderly participants and participants living in urban areas were included in this study compared to the overall Ghanaian demographics. An explanation for this is that patients who use medicines that are distributed by official HCFs is not a proper reflection of the general population of the country. Apart from that, most HCFs in Ghana are located in urban areas (27) and the rural-urban migration makes it difficult to determine if someone lived in an urban or rural area (37). The population sample of the survey covers the full formal Ghanaian health care delivery system but excludes data from patients who buy medicines from unlicensed medicine sellers, since these were not included in the study. A limitation of the study is that only patients that had experienced an ADR were included in the qualitative part of the study. It can be assumed that these participants had more knowledge about ADRs compared to participants that did not experience an ADR before. Also, participants who were not aware of the existence of ADRs were not asked any further questions in the survey. This could have led to an overestimation of the number of patients that experienced an ADR and patients that are aware of the PRS. Another limitation is the possibility of receiving socially desirable answers from the participants. However, the researchers tried to prevent this by asking open and neutral questions and not telling the participants too much about the aim of the study.

CONCLUSIONS

Most Ghanaian patients are aware of ADRs, but especially participants that are older, low educated and live in rural areas seem less likely to be aware of ADR. Moreover, lower educated patients seem to fall short on recognizing ADRs. Incidence of ADR-reporting to HCWs is high among Ghanaian patients. However, most of them appear unaware of or unable/unwilling to use formal national channels for ADR reporting like the Ghana-FDA PRS. Patients appear driven by personal benefit in reporting ADRs instead of communal benefit which may be due to low awareness of the PRS. There are multiple obstacles that hamper patient reporting of ADRs in Ghana which warrant further attention to increase patient reporting of ADRs. Further studies on information

provision about ADRs and ADR reporting by medicine dispensers and the impact of different regulatory measures on the patients' knowledge of ADR reporting and the PRS could help overcome some of these obstacles.

ABBREVIATIONS

ADR: Adverse Drug reaction; FDA: Food and drug Authority; HCF: Health Care Facility; HCW: Health Care Worker; KNUST: Kwame Nkrumah University of Science and Technology; MAH: Market Authorization Holder; MoH: Ministry of Health; PRS: Patient Reporting System; SPSS: Statistical Package for the Social Sciences; SSA: Sub-Saharan Africa; WHO: World Health Organisation

DECLARATIONS

Ethics approval and consent to participate

The research protocol was reviewed and approved by the Committee on Human Research, Publications and Ethics of the Kwame Nkrumah University of Science and Technology (KNUST), reference number: CHRPE/AP/481/16. Verbal informed consent was sought from the participants in the survey and written consent was sought from the participants in the in-depth interviews. The consent form was read to participants with low literacy and they signed with a thumbprint.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests.

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Authors' contributions

TGJ, HHA and JH conceived and designed the study. TGJ conducted the data collection and analysis. HHA supervised the study. TGJ and HHA contributed equally to interpretation of the results and writing of the manuscript. JH, AKM and ANOD

were actively involved in the study progress and revised the manuscript critically. All authors approved the final version of the manuscript.

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CHAPTER 3.2

EVIDENCE BASED PHARMACOVIGILANCE FOR MEDICINES USED IN PUBLIC HEALTH PROGRAMMES IN AFRICA

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ABSTRACT

Pharmacovigilance in Africa has grown sharply this millennium with the number of African countries joining the World Health Organisation (WHO) Programme for International Drug Monitoring having increased from just 5 in the year 2000 to 35 in 2017. However, published information indicates that Africa's contribution of individual case safety reports (ICSRs) to the WHO ICSR database (VigiBase) is paltry currently standing at less than 1% of the >14 million ICSRs in VigiBase. Moreover, there is little evidence of African countries collecting, analysing and using data from their settings to inform pharmacovigilance and drug safety decisions in their own countries. The huge doses of medicine and vaccines deployed for public health programmes including those against malaria, tuberculosis and HIV/AIDS as well as those for infant immunisation against preventable diseases means that there is opportunity to collect real-world data in relation to these medicines and vaccines. Spontaneous reporting may not necessarily be the best approach in the various African countries considering the high under-reporting associated with all spontaneous reporting schemes globally. However, there are opportunities to utilise more active pharmacovigilance approaches including cohort event monitoring and targeted spontaneous reporting to improve collection and use of safety data in Africa to improve patient care, especially in public health programmes in Africa.

INTRODUCTION

The thalidomide tragedy and the resulting global actions spearheaded by the World Health Organisation (WHO) led to World Health Assembly (WHA) Resolution 16.36 which invited "Member States to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use" (1). This WHA culminated in the establishment of the WHO Programme for International Drug Monitoring (PIDM) in 1968 with 10 participating full member countries. None of the 10 founding members of the programme were from Africa and it took nearly a quarter of a century before the first 2 African countries (Morocco and South Africa) joined the WHO Programme for International Drug Monitoring in 1992. Currently, the PIDM has 125 member countries 35 of whom are from Africa. Figure 1 shows the growth of African membership in the WHO Programme since its inception. As shown in the graph, most of the countries from Africa joined relatively recently and the contribution of African countries to the WHO individual case safety report (ICSR) global database of spontaneous reports, VigiBase™ is extremely low with only 0.88% of the 11,824,804 reports being contributed by African countries as at the end of September 2015 (2) Pharmacovigilance does not only involve the collection and submission of ICSRs to VigiBase™. It includes several other activities including signal generation and management, risk management and minimization, communication with the public, patient safety, medication errors prevention and generally taking action to assure public health and safety in so far as the use of medical products is concerned. Studies however indicate that pharmacovigilance in Africa is weak – from the all perspectives including systems, legislation, structure and activities (3). It is important to highlight that prior to 2000, most countries in Africa had to contend with chronic shortage of medicines, weak and non-existent supply chains for medicines and other health commodities and extremely limited financial resources to make any difference (4). In such an environment, pharmacovigilance, however laudable it is had to take a back stage: after all what is the point of starting a safety monitoring system if there are no products to be monitored? It was only when access to medicines started increasing that the stark reality of absent safety monitoring systems was identified leading to calls for collaboration to ensure that all developing countries including those in Africa develop pharmacovigilance systems to protect their populations from medicinal product associated harms (5).

The adoption of the millennium development goals by the United Nations in 2000 provided increased funding to tackle several health and social problems. Funding was therefore provided to several low and middle income countries to combat priority diseases. The growth in pharmacovigilance in Africa was therefore spurred by the increased funding for public health programmes, typically those designed to fight HIV/AIDS, tuberculosis and malaria and the Global Fund against HIV/AIDS, TB and

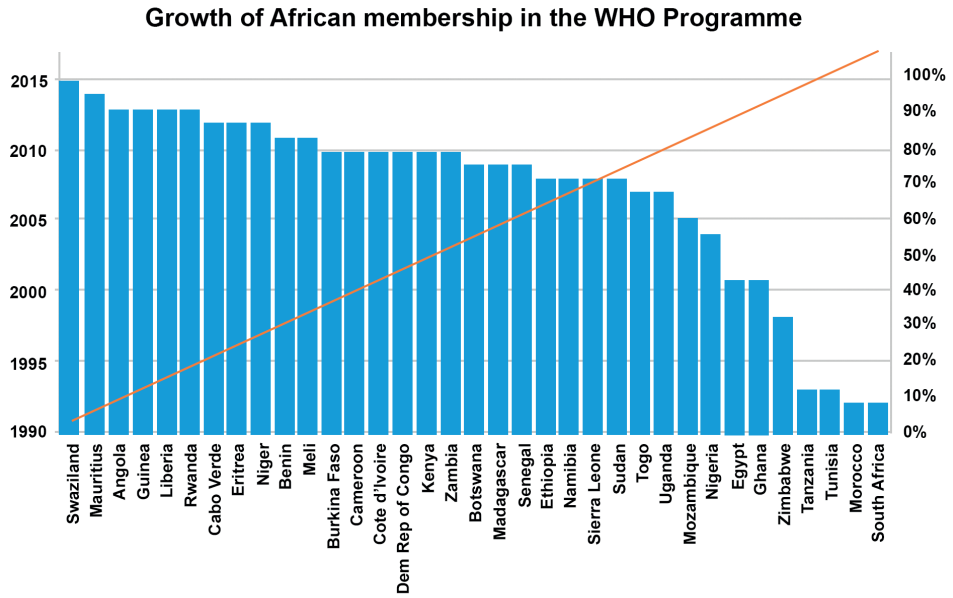

Figure 1. Growth of African membership in the WHO programme

Malaria (Global Fund) remains one of the main sources of funding for public health programmes and pharmacovigilance in Africa (6). In addition, initiatives like the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the US Presidents Malaria Initiative (PMI) (7) have also provided huge financial support for public HIV/AIDS care (8) and for malaria control. The Bill and Melinda Gates Foundation has also been a good and stable source of financial support for public health programmes and for the projects to improve pharmacovigilance in Africa, a recent one being the INDEPTH Network for Effectiveness and Safety Surveillance (INESS) platform which undertook one of the few focused large scale phase IV studies of antimalarials in Africa (9). The interest of the BMGF for safety surveillance of products in Africa and other low and middle income countries (LMICs) led the Foundation to convene a Safety Surveillance Working Group (SSWG) which produced a report on how safety surveillance could be carried out in Africa and other LMICs. The SSWG poignantly recommends among other things that "approaches towards post-market safety surveillance in Africa need not mirror the approaches embarked upon by Western and industrialised countries" (10). This is an acknowledgement of the fact that the systems in Africa have developed differently from those in developed countries and the continent most likely provides opportunities to develop innovative, cutting edge approaches for global pharmacovigilance based on the fact that it can learn from the history of failures and successes in existing developed country pharmacovigilance systems and then utilise the vast array of contemporary tools and technologies to develop responsive, cost-

effective as well as rigorous processes and systems for real-life safety monitoring of medical products. For example, the pharmacovigilance systems in Africa have already started relying on the use of cell phones to collect data from patients rather than rely on paper-based systems. The extensive use of mobile phones across Africa has already changed the way pharmacovigilance studies are undertaken with contact and follow-up occurring by use of cell phones rather than the traditional home visits that were expensive and challenging. Evidence from current studies show that mobile phones are a feasible and realistic approach for pharmacovigilance and provide robust data in prospective studies (11). These initiatives are exciting and the full array of tools and methods that can be used to generate robust post-marketing safety data in Africa is yet to be known. The full realisation of the potential of Africa to provide innovative globally acceptable solutions for pharmacovigilance will take time to manifest but it is important to analyse the current approaches towards pharmacovigilance in Africa with a focus of products used in public health programmes. Of relevance is the level to which pharmacovigilance decision making in Africa has been driven by evidence whether locally generated or foreign and to examine the way such evidence has been obtained whether through traditional pharmacovigilance approaches or by the use of newer methods and tools.

PUBLIC HEALTH PROGRAMMES IN AFRICA AND PHARMACOVIGILANCE

In all countries in Africa, national governments, in collaboration with development partners like the WHO, have established formal public health programmes to spearhead the fight against endemic diseases. Most countries therefore currently have National AIDS/HIV Control Programmes (NACP), National Tuberculosis Control Programmes (NTCP) and National Malaria Control Programmes (NMCP). In addition, these countries have Expanded Programmes on Immunization (EPI) which are responsible for national childhood immunization programmes. The EPI and the various disease control programmes are responsible for the deployment of hundreds of millions of doses of vaccines and medicines to hundreds of millions of people annually. However, most of these programmes and their activities are not associated with verifiable pharmacovigilance systems: concerns have therefore been raised on the ethics of deploying millions of doses of medical products to vulnerable populations without any robust safety surveillance programme. These concerns have led to several initiatives aimed at improving pharmacovigilance in Africa. This was definitely a factor that has led to increasing numbers of African countries joining the WHO Programme for International Drug Monitoring, and the relative sharp increase in the number of ICSRs from Africa in VigiBase (2) though the absolute numbers are still extremely low for a continent of nearly 1.5 billion people. In addition to the relative increase in the number of ICSRs being reported from Africa, there has also been an

increase in the number of peer-reviewed publications relating to pharmacovigilance and/or the safety of medicines and vaccines used in public health programmes in Africa (12-16).

This chapter provides an overview of the state of play of pharmacovigilance and safety surveillance in public health programmes in Africa with a focus on 4 public health programme areas namely: malaria, HIV/AIDS; tuberculosis; and immunization. This does not mean that other public health programmes e.g. those for the control of neglected tropical diseases or non-communicable diseases etc. are less important or do not require pharmacovigilance. Rather, it is to examine pharmacovigilance in these 4 major areas with a view of shedding light on the evidence that may exist and how that evidence is being utilised in pharmacovigilance in Africa. The high burden of malaria, HIV/AIDS and tuberculosis in Africa means that most medicines are used to combat these conditions. Pharmacovigilance of these products is therefore key as is the safety monitoring of vaccines used in childhood immunization programmes since these vaccines are administered to nearly all children born on the continent making the need for a robust safety surveillance system critical and non-negotiable.

PHARMACOVIGILANCE OF ANTIMALARIALS IN AFRICA

In early 2000, the WHO and other agencies called for a change in national malaria policies and treatment options due to widespread parasite resistance to the main drugs being used in Africa – chloroquine or a combination of sulfadoxine+pyrimethamine (SP) (17). The new recommendation was to use artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria. This shift in malaria policy provided a need and also an opportunity to establish PV systems to monitor the safety of the ACTs particularly given the limited knowledge of the adverse drug reactions profiles of these products in Africa (18). In the process, the PV of antimalarials became the pathway for several countries to establish national PV systems. Indeed, the first concerted African training programme on PV was held in 2003 in Lusaka, Zambia by the malaria and PV departments of WHO (19). Though malaria was the pathway for the establishment of any pharmacovigilance system at all in most countries, the WHO and national authorities were naturally keen that any PV system served the whole country and not just malaria control programmes. In addition, the funds provided especially by the Global Fund for the policy change also represented an opportunity to obtain modest funding to start PV activities which had hitherto had no funds at all whatsoever. Subsequently, the US President's Malaria Initiative (PMI) as well as the Roll Back Malaria Programme (RBM) all contributed towards the building of PV centres and systems in Africa though uptake of these resources by countries was very weak (18). In the past few years, it can be argued that PV of antimalarials has enabled PV in Africa to be firmly entrenched.

The first signal from spontaneous reporting in Africa was in relation to an ACT – extrapyramidal symptoms in relation to the use of the combination of

amodiaquine+artesunate (20). This signal was raised solely from data from spontaneous reporting systems in Africa. The signal has since been confirmed and the summary of product characteristics now lists extrapyramidal symptoms as one of the expected adverse effects associated with the use of amodiaquine+artesunate (20). The WHO has also provided support from active studies usually cohort event monitoring (CEM) in Africa and there are publications sharing the experiences gained in these studies (21). The basis for the use of CEM is the fact that spontaneous reporting of ADRs provides very little individual case safety reports. Therefore, in order to obtain real-world data relating to the safety of antimalarials as used in the general population the realistic option is to use active pharmacovigilance approaches including the recruitment and follow up of patients as occurs in CEM. CEM, when undertaken in the African context involves the prospective identification and recruitment of patients on the medication of interest and then recording any adverse events that occurred post medicine administration or intake. This is quite different from Prescription Event Monitoring (PEM) as in this case it is patients who are followed up. This is a pragmatic approach as record-keeping is poor in Africa making the traditional PEM all but impossible. CEM is therefore a more realistic and useful approach for collecting safety data in Africa. Cohort (9, 22) and drug utilisation (23) studies have been carried out in relation to antimalarials. However, when one examines the WHO ICSR database, VigiBase, it becomes very obvious that the data from most of these studies are not submitted to the WHO hence there is much more safety information on antimalarials in peer-reviewed journals than there is in the WHO database. This may be because the regulatory environment did not impose mandatory requirements of ICSRs to the national drug regulatory authorities or, if they did then the enforcement is variable. The lower numbers of ICSRs in VigiBase compared to what is in the published literature may not just be an African phenomenon but rather global and needs addressing especially as no published studies exist to quantify the scale of the issue.

In relation to ICSRs to antimalarials in Africa, one study actually calculated that Africa contributes just over 1% of ICSRs to antimalarials in VigiBase (18), a situation which is worrying considering that Africa bears the greatest burden of malaria and most antimalarials are used in Africa. This poor reporting of ICSRs from Africa limits the ability of reporting systems in Africa to undertake systematic signal detection in stark contrast to systems in developed countries which are able to detect signals through their reporting systems. In addition to the increasing usage of ACTs to treat uncomplicated malaria, the use of antimalarials in Africa is increasing sharply as older products are being used for newer purposes. For instance, most countries now give SP to mothers as part of "Intermittent Preventive Treatment of Malaria in pregnant women (IPTp) (24) or infants (IPTi) (25). A combination of amodiaquine and SP is also given to children as part of Seasonal Malaria Chemoprophylaxis (SMC) (26). For severe malaria, a very serious condition which can be quickly fatal, the WHO

now recommends the use of injectable artesunate instead of parenteral quinine due to safety concerns (27). Despite these massive policy changes and increased usage of medicines outside their original licensed indications, safety data collection remains poor. It is not known to what extent these safety data have been analysed by the global malaria community to inform policy though individual publications are emerging including those mentioned previously. The newer strategies for malaria elimination and changes in global malaria policy makes it necessary and imposes a high moral obligation to have systems to collect rigorous data on these products especially when usage is for malaria prevention and not treatment. As more and more countries focus on malaria eradication and elimination anti-malarial drugs will focus extensively and will need to be monitored closely. This is because as populations witness less malaria, they will become very intolerant of any ADRs to antimalarials and will have very high safety expectations of antimalarials just as is occurring in the vaccine world. The WHO has demonstrated the importance the global community places on safety surveillance of antimalarials and has insisted for more safety and programmatic data in relation to the novel malaria vaccine RTSS,AS01 (Mosquirix), even though the product has received a Positive Scientific Opinion from the European Medicines Agency (EMA) under the so-called Article 58 process (28). The studies to be performed have been deemed as "post authorisation safety studies" by the EMA and will focus on collecting data on both safety and effectiveness of the vaccine. When completed, these studies will constitute some of the most rigorous data-driven studies on antimalarial products in Africa and may offer an approach towards new products for malaria safety surveillance in particular and pharmacovigilance in Africa in general.

Another example is the CEMISA study (clinicaltrials.gov identifier NCT02817919) which is funded by the Medicines for Malaria Venture (MMV) and sponsored by the African Collaborating Centre for Pharmacovigilance to collect real-world medicine safety and utilisation data in 4 African countries (Ethiopia, Ghana, Malawi and Uganda) and which represents one of the first ICH-GCP post-approval real-world studies on a product for treating severe malaria. Other studies are also getting underway including studies on Pyramax™, an antimalarial granted positive scientific opinion by the European Medicines Agency as part of its Article 58 procedure in support of the World Health Organisation. The fact that injectable artesunate is being examined as an investigational new drug in the US (29) for the treatment of severe malaria shows how data from Africa will inform global policy. This makes it imperative for real-world data collection and analysis systems in Africa to be rigorous and ICH-GCP compliant.

PHARMACOVIGILANCE AND NATIONAL HIV/AIDS CONTROL PROGRAMMES IN AFRICA

Africa bears the largest burden of HIV/AIDS in the world and, of the estimated 35 million people living with HIV worldwide in 2013, 71% were in sub-Saharan Africa (30).

Massive progress has been made in reducing HIV-associated mortality by the rapid scale up of antiretroviral therapy. Since HIV is now a chronic disease and patients have to be on life-long treatment, safety monitoring has to be undertaken for the products used to manage the primary HIV infection as well as those used to prevent HIV-related opportunistic infections. In addition, there is also a need for pharmacovigilance of products used to treat other endemic diseases as well as those for treating the increasing cases of non-communicable diseases since interactions between these products and antiretroviral therapies can occur. Hence the pharmacovigilance of antiretroviral therapy in Africa has to include the safety monitoring of anti-retrovirals alone as well as monitor the safety implications of concomitant administration of anti-retrovirals and other medicines e.g. antimalarials, anti-tuberculosis, anti-hypertensive and anti-diabetic medicines. Safety surveillance of anti-retroviral therapy is perhaps the most intense pharmacovigilance activity in Africa.

There are several publications involving the safety monitoring of products used for post-exposure prophylaxis in HIV/AIDS (31) and a lot more on the adverse events associated with anti-retroviral therapy in general (32). In relation to the methods employed, both passive and active pharmacovigilance approaches have been used with spontaneous reporting and targeted spontaneous reporting as well as cohort event monitoring (CEM) being used (16, 33). Most of the studies undertaken so far have been stand-alone with only the IeDeA consortium undertaking multi-country post-approval studies. The International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration is however not really focused on pharmacovigilance but rather on epidemiology and safety is not the primary endpoint in this collaboration even though the collaboration encourages treating physicians in the various IeDeA sites to collect adverse event information on its electronic capture tools. Very little of this data finds its way to the WHO database depriving the world of real-world safety data from multiple countries and sites. Despite the intense research and publication currently taking place on the safety of anti-retrovirals in Africa, it appears most of the data is not shared with national authorities for onward transmission to the WHO database, VigiBase. Whilst more than half of the ICSRs from Africa are in relation to products for managing HIV/AIDS they remain a tiny fraction of the ICSRs in relation to these products. Thus, at the end of September 2015, there were a total of 2,962 ICSRs in relation to nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and antivirals for the treatment of HIV infections in the WHO database compared to 105,089 for the same products for the rest of the world (2). This is despite the fact that Africa has the largest global burden of HIV/AIDS and consumes the largest volume of these products. In relation to WHO policies for the treatment of HIV/AIDS, majority of the evidence has come from clinical trials rather than from post-market surveillance though post-approval clinical trials in Africa were key in changing treatment recommendations for children e.g. early treatment of children (34) with HIV and early time-limited treatment of HIV in children vs. deferred

treatment (35). In relation to safety, data from Africa seem to have contributed little in the signals raised in relation to several antiretroviral products whether used alone or in combination

For instance, abacavir hypersensitivity appears to have been more and better described in studies from developed countries than from Africa. Similarly, the risks of myocardial infarction with nelfinavir, anaemia with zidovudine, rashes with nevirapine and lactic acidosis with stavudine appear to have all been identified from clinical trials and post-approval studies from outside Africa (36). Nonetheless, a few studies in Africa have attempted to provide local data to justify local policy e.g. data showing the safety of post-exposure prophylaxis with anti-retrovirals (31) or the influence of modification of anti-retroviral therapy on the ADRs experienced by patients (32). The large number of trials involving anti-retrovirals that has taken place in Africa gives the continent a good human resource base for clinical evaluation of products. However, it appears there is a dearth of published safety data when it comes to post-authorisation safety surveillance. This may be due to several factors including lack of investment for human and technical resources to undertake routine pharmacovigilance and generate the evidence needed to assure a continuing positive benefit-risk ratio of marketed products. It may also be that national authorities in Africa rarely use their own data for regulatory decision making relying instead on the decisions of stringent regulatory authorities like the US FDA or the European Medicines Agency or on decisions made by the WHO. Whichever the case, there is the need for every country to undertake robust PV of all products used in public health programmes including those against HIV/AIDS.

PHARMACOVIGILANCE OF ANTI-TUBERCULOSIS DRUGS

Tuberculosis (TB) provides an area where PV data from Africa has had immediate impact on policy and will continue to do so for some time to come. Most drugs used to manage TB are quite old and in the late 1980s when thiacetazone (available since 1940s) began to cause severe cutaneous reactions in HIV positive individuals in Africa, the WHO recommended its replacement with ethambutol. Thiacetazone is currently no longer recommended by WHO as first-line therapy for TB except in rare and special situations but the experience it provided caused the WHO to call for increased investments in the PV of TB medicines (37). There have been very few new products for TB and the management of TB, especially multi-drug resistant TB (MDR-TB), is extremely challenging especially in environments where HIV is also high. In 2012, the US FDA granted accelerated approval for the use of bedaquiline for managing MDR-TB based on data from phase IIb trials only (38). This is a bold move because it goes against the traditional paradigm of drug development and suggests a new possibility for critical areas in public health. The need for an effective treatment for MDR-TB and the public health considerations allowed the FDA to

approve bedaquiline. The WHO subsequently recommended its usage in national TB programmes but with a clear call for active and robust PV to ensure that more data is collected on its safety, benefits and effectiveness in routine use. The current usage of bedaquiline in public health programmes is therefore essentially a large, global open-label non-randomised phase III study. The collection, sharing and use of safety information in this phase will determine whether this approach of early product release associated with large post-authorisation data collection is feasible, responsible and useful for public health. WHO continues to encourage all national TB control programmes to undertake PV of drugs used in TB and has published guidance to assist in the same. However, compliance by national authorities is variable and there has not been an increase in the ICSRs in VigiBase in relation to anti-TB drugs though there have been a few publications in the literature from other regions of the world (39, 40). Like malaria and HIV/AIDS, there is still a long way to go before real-world post-approval safety data from Africa becomes widely available to inform local, regional and global policy.

VACCINE PHARMACOVIGILANCE IN AFRICA

Pharmacovigilance in Africa is in its infancy but it is far more developed than vaccine pharmacovigilance (Vaccine PV) in Africa. Vaccine PV is a new area, having only been recently defined (10) as an area similar to and yet distinct from "drug PV". The management of data on adverse events following immunization (AEFI) in particular and all data on vaccine PV in general varies from country to country with some countries having separate systems and some having the same. Vaccine pharmacovigilance falls in 2 broad domains in several low and middle income countries including most countries in Africa: the Expanded Programme on Immunization (EPI) which is responsible for national childhood immunizations and the national regulatory authority responsible for licensing vaccines and all other products (41). Both of these agencies collect safety information on vaccines. Where the EPI collects AEFI, is expected that it will be shared with the national regulatory authority but this is rarely the case and the WHO ICSR database has very few AEFI data from Africa. Assessments by the WHO indicate that several countries in Africa do not have even the barest capacity for vaccine safety surveillance (42, 43). The Global Vaccine Safety Blueprint has therefore been developed to ensure that all countries (especially the low and middle income countries of Africa) have efficient vaccine safety monitoring systems (Global Vaccine Safety Blueprint). Despite this weakness, there have been approaches towards real-life safety monitoring of vaccines used in Africa. For instance, in 2003, Dodoo et al (44), undertook an active follow-up study to document adverse events following immunization after a change in EPI policy in Ghana to replace the trivalent Diphtheria-Pertussis-Tetanus vaccine with a pentavalent vaccine containing the following antigens: Diphtheria, Pertussis, Tetanus, Haemophilus influenza type B and hepatitis

B (REF). In 2010, the rapid development and deployment of a vaccine (MenAfriVac) against Neisseria meningitidis serogroup A, the major cause of meningitis outbreaks in sub-Saharan Africa offered the opportunity to develop a responsive and pragmatic system for safety data collection in sub-Saharan Africa (45). During the one-month period in which nearly 400,000 individuals aged 1-29 years (including pregnant women) were immunized in Niger, an enhanced spontaneous surveillance system was put in place to collect AE data during the campaign and up to 6 weeks later. This allowed the collection of 82 suspected AEFIs 16 of them being severe. The authors acknowledged the under-reporting of AEFIs but also identified the opportunity that the campaign provided to develop PV in Niger to international standards. New or newly deployed vaccines in Africa is hence providing an opportunity to strengthen PV in Africa and active PV studies are currently being undertaken in association with the deployment of the rotavirus vaccine (46), the pneumococcal conjugate vaccine (47) and the human papilloma virus vaccine (48) in Africa.

The very low number of ICSRs from Africa in VigiBase shows that the national spontaneous reporting systems in Africa are currently not receiving and/or sharing enough spontaneously reported ICSRs. So even though spontaneous reporting remains the bedrock of PV, other approaches have to be used in Africa. Active approaches, especially cohort event monitoring (CEM) appears to be able to provide rigorous data quickly. However, it appears that data from CEM is not being shared with national regulatory authorities for policy decision making. There is much more safety data from Africa in the published literature than in the WHO database a situation which must change and which requires collaboration between all stakeholders, especially researchers, academia and national drug regulatory authorities.

DISCUSSION AND CONCLUSION

The pharmacovigilance landscape in Africa has changed remarkably since 2000. Whereas there were only 5 African countries who were members of the WHO Programme for International Drug Monitoring in 2000, there are now 35 countries. This increase has been accompanied by increasing establishment of national regulatory authorities as well as increase passing of laws and guidelines for PV and product regulation. Some countries are already asking the pharmaceutical industry to provide periodic safety update reports or similar documents as they would do in ICH countries. In the past, industry could justifiably point out to the absence of structures and infrastructure for PV and hence state its inability to collect and submit African data to African regulators, as well as analyse themselves. That situation has changed rapidly and industry and regulators will have to find means of collecting and submitting safety data in Africa. Some countries including Ghana, Kenya and Nigeria are also demanding that all marketing authorization holders have Qualified Persons for Pharmacovigilance (QPPV) and also establish a complete PV system in line

with the EU Good Pharmacovigilance Practice (GVP) guidelines. Clearly, there will be a lot of activity in the PV front in Africa. The gaps identified in this article especially the low numbers of ICSRs in national databases compared to a high number of safety reports in the scientific literature needs to be bridged. This is important because ADRs from Africa can differ from those of the rest of world as shown by a recent study on angiotensin-converting inhibitors (49). Enforcement of laws is important but it is just one option. Education, training and development of a culture of safety reporting may hold the key to more sustainable success. Data driven PV in Africa is possible and desirable and systems capable of collecting longitudinal data are also needed urgently in Africa. With the deployment of some products for the first time ever in Africa e.g. the malaria vaccine, it is clear that data from Africa will inform global policy and practice. It is therefore essential that the global community works with African countries and African partners to develop robust approaches for the collection and sharing of safety data for the benefits of Africa and the world. This is a responsibility for all stakeholders in PV.

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CHAPTER 4

GENERATING EVIDENCE ON SAFETY AND USE OF MEDICINES IN CLINICAL PRACTICE

CHAPTER 4.1

SAFETY EXPERIENCE DURING REAL-WORLD USE OF INJECTABLE ARTESUNATE IN PUBLIC HEALTH FACILITIES IN GHANA AND UGANDA: OUTCOMES OF A MODIFIED COHORT EVENT MONITORING STUDY (CEMISA)

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ABSTRACT

Background

Injectable artesunate (Inj AS) is the World Health Organisation (WHO) recommended product for treating severe malaria. However, despite widespread usage, there are few published safety studies involving large populations in real-world settings. In this study, we sought to assess the incidence of common adverse events (AEs) following the intake of Inj AS in real-life settings.

Methods

This is a modified cohort event monitoring study involving patients who were administered with Inj AS at eight sites (four each in Ghana and Uganda) between May and December 2016. Patients were eligible for inclusion if they had severe/ complicated malaria and were able and willing to participate in the study. Eligible patients were followed up by telephone or hospital or home visit on Days 7, 14, 21 and 28 after drug administration to document AEs and serious AEs (SAEs). Patients were also encouraged to report all AEs at any time during the study period. The Kaplan–Meier method was used to estimate the proportion of patients with any AEs by end of Day 28. Causality assessment was made on all AEs/SAEs using the WHO/ UMC (Uppsala Monitoring Centre) causality method.

Results

A total of 1103 eligible patients were administered Inj AS, of which 360 patients were in Ghana and 743 in Uganda. The incidence of any AE by the end of follow-up among patients treated with AS was estimated to be 17.9% (197/1103) (95% confidence interval [CI] 15.8–20.3). The median time-to-onset of any AEs was 9 days (interquartile range (IQR) = 4, 14). The top five AEs recorded among patients treated with AS were pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). Most of these top five AEs occurred in the first 14 days following treatment. Regarding the relatedness of these AEs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related. There were 17 SAEs including 13 deaths. Two of the deaths are 'possibly' related to Inj AS, as were three non-fatal SAEs: severe abdominal pain, failure of therapy and severe anaemia.

Conclusion

The incidence of common AEs among patients treated with Inj AS in real-world settings was found to be relatively low. Future studies should consider larger cohorts to document rare AEs as well.

Key Points

Injectable artesunate (Inj AS) is a life-saving medicine used to treat severe Malaria. There are few data on the safety of Inj AS when used in real-world settings, though it has been shown to be well-tolerated in clinical trials.

Safety data obtained from public health facilities in Ghana and Uganda support the safety findings from clinical trials and provide additional evidence for continued use of Inj AS in severe malaria.

INTRODUCTION

Severe malaria is a life-threatening condition responsible for a significant part of the 445,000 global malaria deaths that occurred in 2016 alone (1). When not treated, the case fatality rate for severe malaria can be very high. Severe malaria is the harshest form of the disease. In addition to the symptoms of uncomplicated malaria such as fever, parasitaemia and malaise, severe malaria also manifests with one or more of the following: severe anaemia, acute renal failure, respiratory oedema, hypoglycaemia or coma. Published fatality rates for severe malaria vary widely due to study design, treatment practices and patient types. Fatality rates are typically around 16–20% but rates as low as 2% and high as 100% have been reported (2). With prompt and effective treatment, case fatality rates can fall as low as 10% (2) or below. The current edition of the World Health Organisation (WHO) Guidelines for the Treatment of Malaria (2015, third edition) (3) recommends injectable artesunate (Inj AS) (ATC [Anatomical Therapeutic Chemical] code P01BE03) as the treatment of choice for severe malaria. The SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial) (4) and AQUAMAT (Artesunate Versus Quinine in the Treatment of Severe Falciparum Malaria in African Children) (5) studies showed reductions in fatality of 34.7% and 22.5%, respectively, when Inj AS was used to treat severe malaria instead of injectable quinine. In these studies, the use of Inj AS was also associated with fewer adverse events (AEs) than quinine. Systematic reviews (6, 7) have also demonstrated lower case fatality rates and lower AE profiles with Inj AS than with quinine. For years, parenteral quinine remained the main drug for treating severe malaria, but its usage is associated with problems in reconstitution and administration (8). Quinine needs to be administered slowly as a constant intravenous (IV) infusion, a process which is difficult in most settings. It may also be given intramuscularly (IM) but IM administration is associated with erratic availability and poor clinical outcomes. In addition to these, the use of quinine is associated with several AEs including cinchonism, rashes, rare cardiotoxicity, deafness, hypoglycaemia, dizziness, blindness and even death (9, 10). These factors prompted the WHO policy change and subsequent recommendation for the use of Inj AS for treating severe malaria.

The current data on the efficacy and clinical safety of Inj AS have all been obtained in well-controlled clinical trials or during operational research (6, 11–15). The recruitment of patients in such settings is controlled and patient follow- up and management is stringent in these studies; hence, safety information obtained may not reflect what occurs in real life. There is a dearth of information on the safety of Inj AS when used in real-world (post-approval, routine healthcare practice) settings even though a signal—postartesunate delayed haemolysis (PADH) has been raised following identification of a number of delayed haemolysis cases after treatment with Inj AS (16–18). Inj AS is an extremely important life-saving product in the treatment of severe malaria across all 91 malaria-endemic countries and across all malaria transmission zones (1, 19). It

is used extensively in imported or traveller's malaria in non-endemic countries, where it has been associated with very high reduction in mortality with few reports of drug-related AEs (20). Despite the assurance given by the available studies on the safety of Inj AS, the absence of strong pharmacovigilance systems in countries that use millions of doses of the product annually makes it necessary to undertake appropriate post-authorisation studies in order to better understand its actual safety profile when used in real-world settings. This study was therefore conceived to obtain safety data in relation to Inj AS when used in real-world settings in public health facilities in two African countries where severe malaria may or may not be properly diagnosed (microscopy; rapid diagnostic tests [RDTs]; laboratory measurement of haemoglobin [Hb]) and where facilities for monitoring and follow-up are variable.

The specific objective of the study was to determine the incidence of any AEs that occur up to 28 days after administration of Inj AS for the treatment of severe/complicated malaria during the normal course of clinical practice in the participating health facilities. The findings from this study should contribute to the WHO global individual case safety report (ICSR) database VigiBase™ and facilitate quicker identification of safety signals. Currently, VigiBase™ has very little data from Africa that includes data on antimalarials (21, 22).

METHODS

Study design, sites and patient recruitment

This was a prospective, longitudinal, modified cohort event monitoring study in sub-Saharan Africa (CEMISA) which utilises the principles of prescription event monitoring (23) but with cohorts smaller than the minimum 10,000 patients. The study recruits patients in secondary care settings similar to the approach adopted in specialised cohort event monitoring (24). In this study, the cohort consisted of patients who were prescribed Inj AS for presumed or diagnosed severe malaria between May 2016 and December 2016 in two countries (Ghana and Uganda). The study was undertaken in four public health facilities in Ghana (Princess Marie Louise Hospital and Ridge Hospital, Accra; Kintampo Municipal Hospital, Kintampo and Agogo Medical Research Hospital, Agogo) and four public health facilities in Uganda (Mubende Regional Referral Hospital, Mubende; Jinja Referral Hospital, Jinja; Lira Regional Referral Hospital, Lira and Kagadi Hospital, Kagadi).

Patients were eligible for inclusion if they had severe/complicated malaria (Plasmodia of any species) presumed or diagnosed as per national policies and health facility practice/protocol (3); if they were able and willing to participate in the study; and if they agreed to the schedule for follow-up contact or home visits. Patients were excluded if they had a serious concurrent illness. All eligible patients gave informed consent. For children, informed consent was obtained from parents or a caregiver/guardian.

Case Report Forms (CRFs) were used to record data on each study subject during the study as defined by the protocol. All events that happened in the study were fully documented in the CRF. The CRFs consisted of the day 1A form, drug administration form, follow-up forms (Days 7, 14, 21 and 28), AE form, SAE form and the end of study form. The day 1A form served as the enrolment form on the first day of the study. It was the form used after the participant or representative signed the informed consent to record demographic, medical history and laboratory data. The drug administration form was used to record the drug under investigation administered to the participant and all other concomitant medications. The AE form was used to record all AEs and the SAE form was used to record events that met the seriousness criteria. The Day 7 to Day 28 follow-up forms were used to record the participant's current health status and any new concomitant medications. Finally, the end of study form was used to record the primary reason for the termination from the study. A completed CRF after going through the various validations and data quality checks is then prepared for entry into the study database.

Patients were followed up to document the occurrence of any AEs using standard questions on the follow-up CRFs. Patients were followed up by telephone or hospital or home visit, when possible, on Days 7, 14, 21 and 28 after drug intake (index date) and were asked to report all AEs at any time during the 28-day follow-up period. The 28-day follow-up period was adopted in line with the follow-up period adopted for malaria clinical trials (25) as well as previous studies on the safety of antimalarials (26). No attempt was made to intervene in routine care of any of the recruited patients in the study apart from monitoring the safety of the antimalarial agents administered by the treating clinicians by collecting data from consenting patients directly and sometimes also from their clinical notes. Hb levels, when measured, were also recorded. Any patient with AEs was managed in line with existing standard of care in each of the participating facilities.

Definitions

The following definitions are based on the European Union's Guidelines on Good Pharmacovigilance Practice.

Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical investigation participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Serious AE (SAE)

An SAE means an AE that results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Data collection, drug prescription and dosing

Routine clinical practice in malaria-endemic countries requires immediate treatment of patients with suspected clinical malaria in line with WHO Guidelines for the Treatment of Malaria (3). Treatment of severe malaria occurs usually in in-patient settings. All study participants were recruited from hospitals. The implication for this study, therefore, was that most patients had started treatment before being recruited into the study. IM/IV artesunate was administered as per normal practice in the treating institutions. The actual dosage and duration of treatment as well as any concomitant medications were extracted from the patient's clinical notes and recorded on the study CRFs. The WHO recommendation (3) for treating severe malaria is to ''treat all adults and children with severe malaria (including infants, pregnant women in all trimesters, lactating women) with intravenous or intra- muscular artesunate for at least 24 h. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT [artemisinin-based combination therapy]''. We also collected data on mode of malaria diagnosis (i.e. clinically, microscopically or by the use of RDTs). Other co-variables collected included laboratory investigations conducted (including Hb measurements). Data were entered, managed and stored in a specially created version of MedSpina™, an in-house electronic health records system that allows clinicians and other health workers to collect patients' data, including laboratory results, to facilitate patient care.

Outcome and causality measurement

The outcomes measured in the study were all AEs temporarily associated with the intake of Inj AS, including deaths and other SAEs. Assessment of causality included, where available, the level of parasitaemia as well as any concomitant medications administered. Since this was a non-interventional study, there was no systematic laboratory investigation to document AEs. However, all events reported or available in the patient's notes, including laboratory data, were extracted and recorded in the CRFs. Using the WHO/UMC (Uppsala Monitoring Centre) causality method, a physician and a pharmacist not involved in the direct care of the participants assessed the relatedness and causal link of the medicine to the AEs.

Sample Size Calculation

The study was powered to estimate the incidence of AEs with a certain level of precision in Ghana and Uganda. We assumed that the incidence of any AEs in

the Ghanaian and Ugandan population was, on average, 20%. We therefore required a total of 3164 patients in the two countries to produce a two-sided 95% confidence interval (CI) for the ratio of population proportions with a width that is equal to 0.200 when the estimated sample proportion decreases to 0.12 and the ratio of the sample proportions is 0.60. Due to available funding, we planned to enrol a cumulative sample size of 1000 patients receiving Inj AS from all participating countries in the first part of this study with the additional number of 2164 expected in the second part. The 1000 patients produces a two-sided 95% CI with a width equal to 0.050 when the incidence of any AE is 20% as we have assumed.

Data analysis

We summarized patients' characteristics using proportion (nominal scale variables) and mean or median (interval scale variables). We calculated the incidence of any AEs as the total number of any AEs recorded by end of follow-up divided by the total number of patients treated with AS and who completed the study. The Kaplan–Meier method was used to estimate the proportion of patients with any AEs by the end of Day 28. The date of treatment was considered as the origin (i.e. the date the patient was at risk of any AE). The patient was censored at the date the patient was last seen (i.e. lost to follow-up) or at the end of the study without any AE.

Since the study was designed to have a cumulative sample size of 1000 patients on Inj AS from all participating countries (Part 1), with the eventual number of 3164 expected in Part 2, we considered site (country) as a fixed effect and therefore we did not present results for each country. All analyses were performed using STATA® 14 MP (StataCorp, College Station, TX, USA). Case summaries were also presented for all SAEs, including deaths and their relatedness to Inj AS as well as the causality assessment gradings.

RESULTS

Characteristics of participants and treatment received

A total of 1262 patients were screened, of whom 46 were excluded for declining to participate in the study (Figure 1). Of the 1216 eligible patients, 25 were lost to follow-up and 88 were treated with either artemether or quinine, making them ineligible for analysis. There were 1103 patients who were treated with Inj AS (360 in Ghana and 743 in Uganda) (Table 1) and completed the study. The median age of patients was 3.9 years (interquartile range [IQR] = 2.1, 9) and the median weight was 13kg (IQR=10, 20) (Table 1).

Patient follow-up and recording of haemoglobin readings

Most patients were followed-up by way of telephone calls. Of the 1103 individuals treated with Inj AS, 894 (81.1%) were followed up by telephone calls, 88 (8.0%) by

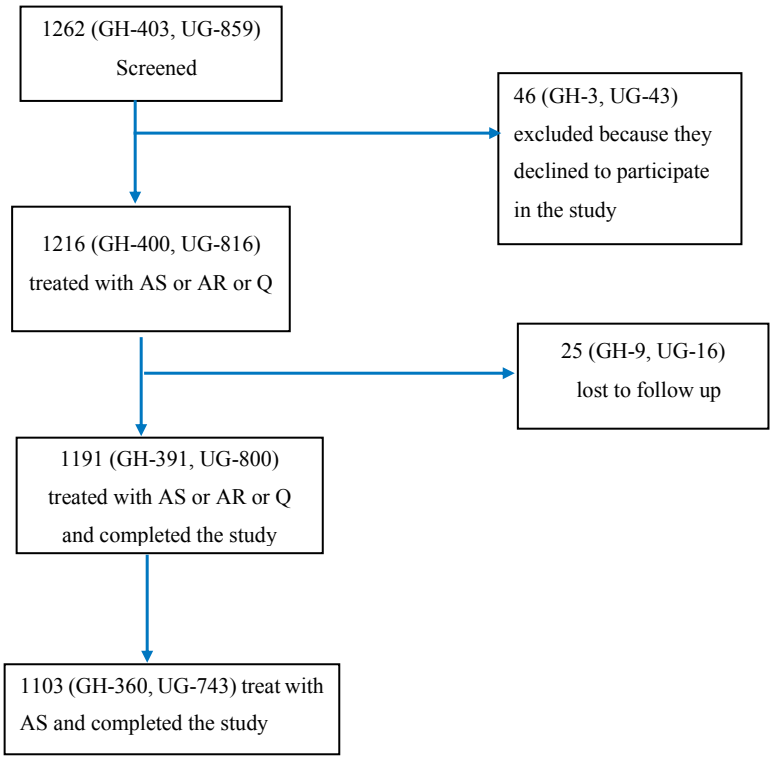


Figure 1. Patient flow. AE adverse event, AR artemether, AS artesunate, GH Ghana, Q quinine, UG Uganda

home visits and 63 (5.7%) by hospital visits. In 58 (5.3%) follow- ups, the mode was not indicated. In relation to Day 14 follow-ups, 874 (79.2%) were by telephone calls, with 88 (8.0%) and 82 (7.4%) being by way of home visits or in hospital, respectively. Day 21 follow-ups followed a similar pattern, with 932 (84.5%) by telephone calls, 82 (7.4%) by home visits and 38 (3.4%) by hospital visits. In relation to Hb readings, there was marked differences between Ghana and Uganda. In the Ghana sites, baseline Hb was measured for 327 of the 360 patients, representing 90.8% of the patients. Seven patients in Ghana had Hb values recorded on both Day 0 and Day 14, and in all these cases the Hb values rose from baseline, indicating remission of anaemia. In Uganda, only 106 (14.3%) of the 743 patients had Day 0 Hb recorded and only one patient had Day 14 Hb recorded.

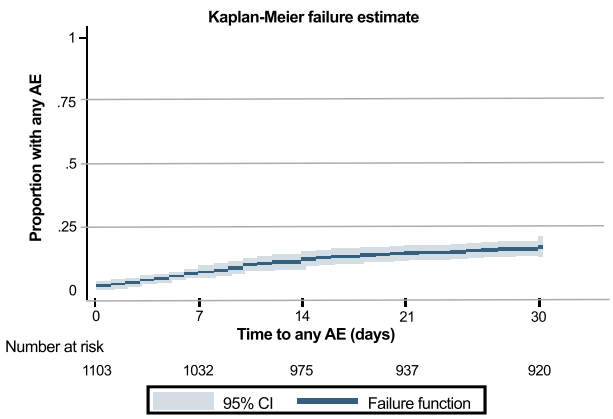
Incidence of any AEs

The incidence of any AE by the end of follow-up among patients treated with Inj AS was estimated to be 17.9 (i.e. 197 of 1103) (95% CI 15.8–20.3) (Table 1 and Figure. 2).

Table 1. Incidence of any adverse events by baseline characteristics of patients, 2016

Characteristics	Median (IQR)	Number of patients (% of total)	n (%) who had any AE	95% CI
Sex		540	96	14.8-21.2
Female		563	102	15.1-21.5
Age(years)	3.9(2,9)			
<5		654 (59.3)	115 (17.6)	14.8-20.7
5-9		186 (16.9)	24 (12.9)	8.8-18.5
10-19		61(5.5)	10(16.4)	9.0-27.9
15–19		40 (3.6)	10 (25.0)	14.0–40.6
20–24		46 (4.2)	10 (21.7)	12.1–35.9
25+		114 (10.3)	29 (25.4)	18.3–34.2
Missing		2 (0.2)		
Weight (kg)	13 (10, 20)			
<10		255 (23.1)	49 (19.2)	14.8–24.5
10–19		470 (42.6)	72 (15.3)	12.3–18.9
20–29		105 (9.5)	14 (13.3)	8.1–21.3
30+		184 (16.7)	36 (19.6)	14.4–25.9
Missing		89 (8.1)		
Time-to-onset of AE (days)	9 (4, 14)			
Site				
Ghana		360 (32.6)	125 (16.8)	14.3–19.7
Uganda		743 (67.4)	73 (20.3)	16.4–24.8
Pregnant				
No		1067 (96.7)	193 (18.1)	15.9–20.5
Yes		68 (3.3)	5 (13.9)	5.9–29.3
Total		1103 (100)	197 (17.9)	15.8–20.3

AE adverse event, CI confidence interval, IQR interquartile range



AE adverse event, CI confidence interval

Figure 2. Proportion of patients with any adverse events by time, 2016: Kaplan-Meier failure estimate

The median time-to-onset of any AEs was 9 days (IQR = 4, 14) (Table 1). The top five AEs recorded among patients treated with Inj AS were pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%) (Table 2 and Figure 3). Most of these top five AEs occurred in the first 14 days following treatment (Table 2). Regarding the relatedness of these AEs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of abdominal pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related.

Table 2. Top five adverse events by sex and time-to-onset among patients treated with injectable artesunate at all sites, 2016

Number of patient treated with Inj AS		AE [n (%)]				
		Pyrexia	Abdominal pain	Diarrhoea	Cough	Asthenia
Sex	1103					
Female	540	16(3.0)	13(2.4)	6(1.1)	9(1.7)	8(1.5)
Male	563	22(3.9)	14(2.5)	13(2.3)	7(1.2)	8(1.4)
Time-to-onset AE(days)	198					
0-7	77	11(14.3)	12(15.6)	6(7.8)	5(6.5)	9(11.7)
8-14	58	12(20.7)	4(6.9)	8(13.8)	5(8.6)	6(10.3)
15-21	27	7(25.9)	2(7.4)	3(11.1)	4(14.8)	1(3.7)
22-28	36	8(22.2)	9(25.0)	2(5.6)	2(5.6)	0(0.0)
Total	1103	38(3.5)	27(2.5)	19(1.7)	16(1.5)	16(1.5

AE adverse event, Inj AS injectable artesunate

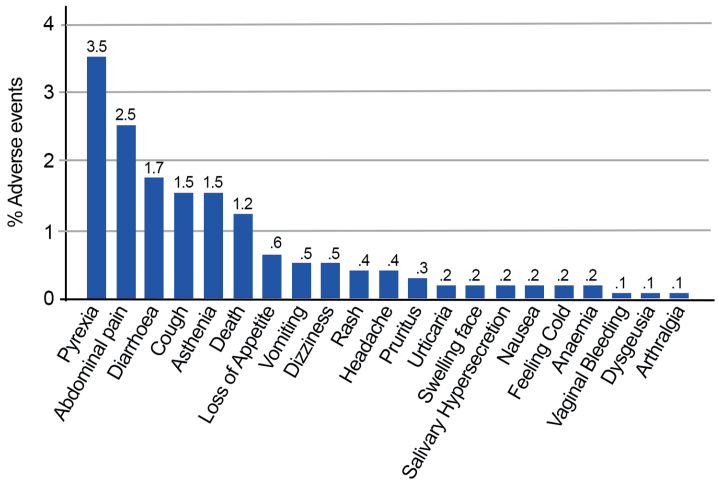


Figure 3. Adverse events among patients treated with injectable artesunate at all sites 2016

SAEs including deaths

During the study, 17 AEs were considered to be serious; 13 of these led to death. The deaths and the four other SAEs are described in Table 3. Four of the deaths occurred in seriously ill patients who were transferred from the hospital to their home with no further follow-up information due to the reluctance of carers/guardians and/or family members to provide any further information. Two others had no post- mortem information even though follow-up information with family members confirmed death.

DISCUSSION

This is the first large-scale post-approval safety study on Inj AS. It involved over 1100 patients who were exposed to at least one dose of Inj AS in the participating public health facilities in Ghana and Uganda. The majority of the participants were children, with 59.3% being less than 5 years old. Inj AS was very well-tolerated among the study population even though nearly one-fifth of participants reported at least one mild to moderate AE. The most common AEs reported in both countries included pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). The relationship between Inj AS and most of these events were classified as 'possible' following case causality assessment. There were 13 all-cause deaths reported in this study, giving an all-cause death rate of 1.2% (13/1103). Two of the deaths could be 'possibly' related to Inj AS. There were four other SAEs in addition to the deaths. Three of the non-fatal SAEs were 'possibly' related to Inj AS. Overall, the safety profile of Inj AS in the study population was favourable and comparable to that documented in the SEAQUAMAT and AQUAMAT studies.

Table 3. Death and other serious adverse events reported in patient treated with injectable artesuante

Event type	n	Relationship to Inj AS intake
Event	13	4 of the 13 deaths did not have SAE specified and patients died outside the hospital with little information on follow-up. These reports are classified as 'unassessable'. 2 of the remaining 9 fatal SAEs (severe anaemia in a 22-month-old female and severe anaemia in a 20-month-old female) are causally assessed as 'possible' in relation to Inj AS intake. These SAEs are classified as 'related' to Inj AS, though disease and other conditions could also explain these SAEs. The remaining 7 fatal SAEs (multi- organ failure, severe respiratory distress, abdominal distension, asthenia, sickle cell disease, severe anaemia, pulmonary tuberculosis) are unrelated to Inj AS intake
Other SAEs	4	3 of the 4 SAEs-severe abdominal pain in a 42-year-old female; failure of therapy and severe anaemia in a sickle cell disease patient are causally assessed as 'possible' in relation to Inj AS intake and thus related to Inj AS. 1 case-threatened abortion is considered to be causally assessed as 'unlikely' to be attributable Inj AS intake and is thus unrelated

Inj AS injectable artesunate, SAE serious adverse event

The results obtained from this study are similar to the findings from clinical trials of Inj AS, including SEAQUAMAT and AQUAMAT studies. The overall incidence of AE is similar to that listed in the public assessment reports (PARs; Part 4: Summary of Product Characteristics) for Inj AS, as published by the WHO (27). The PAR lists the following among the possible common (1–10 in 100 patients) AEs related to Inj AS: cough, diarrhoea, abdominal pain and 'flu-like' effects (including fever, tiredness, bone and muscle pain). These AEs are, however, also symptoms of malaria and severe malaria, making case causality assessment complex. Nonetheless, the study findings provide validation for the safety profile of Inj AS as recorded in the PAR. This study recorded a lower proportion of deaths than the AQUAMAT and SEAQUAMAT studies. In the AQUAMAT study, 8.5% of the 2712 patients in the artesunate arm died (230 African children), whilst 15% of the 730 patients in the artesunate arm of the SEAQUAMAT study died (107 Asian patients) (4, 5). It is important to state that, in contrast to our study, the SEAQUAMAT and AQUAMAT studies involved patients who had been clinically diagnosed with severe malaria. In our study we did not apply a strict definition of diagnosis of severe malaria as the aim was to follow patients who had been administered Inj AS in the 'normal course of clinical practice'. It is, therefore, possible that several of the cases in our study are not necessarily severe malaria, a serious disease with relatively high mortality. The lower mortality of 1.1% obtained in this study com- pares with a similar study (28) in Africa where an overall mortality of 1.03% (2/194) was recorded, though it must be stressed that reported mortality in severe malaria varies widely due to differences in practices, including not applying strict criteria for the definition of severe malaria (29). Our study had two reports of severe anaemia which may be potential cases of PADH. PADH occurs 14 days after artesunate intake and has other features. However, the absence of pre-Day 14 Hb readings in the two cases made a definite diagnosis of PADH fundamentally impossible.

This work has provided evidence indicating a favourable toxicity profile of Inj AS in real-world settings and one that is similar to that observed in earlier studies. However, it suffered from the limitations of most real-world studies. For instance, patients were enrolled if they had been administered at least one dose of Inj AS, presumably for the treatment of severe malaria. However, the majority of the patients were enrolled without any Hb readings and diagnosis of severe malaria was purely based on RDT and/ or microscopy. Even in cases where microscopy or RDT showed absence of malaria parasites, the patients were still administered Inj AS. The safety profile of Inj AS would not necessarily be expected to be different in patients with the potentially deadly severe malaria than in patients without severe malaria, though the outcomes of treatment may differ. Another limitation of the study was the absence of baseline and Day 14 Hb values. Whilst there were 327 (91%) Day 0 Hb readings in Ghana, there were only seven (1.8%) Day 14 Hb readings in this same cohort. In Uganda,

there were only 106 (14.3%) Day 0 Hb readings and one (0.1%) Day 14 Hb reading. Thus, in most of the participating facilities, most patients did not have more than one recorded Hb reading from the time of administration of Inj AS to the time the patient exited the study. This made it impossible to know whether there had been any drug-related changes in Hb values post-administration. Thus, even though very low levels of Hb were recorded in a few patients on Day 14, it was impossible to know whether this represented an existing severe anaemia or an actual fall due to Inj AS and which could thus have been a potential case of PADH. Another challenge in this real-world study was not being able to obtain follow-up information on four patients who died at home. The family/carers were not willing to provide any information, making it impossible to make any causal relationship. Finally, this study was not powered to detect rare AEs since the sample size of 1103 can only detect common AEs. It will be important to expand the study further in order to capture rare AEs in real-world settings. However, this follow-up study should, as a matter of ethics and for public health considerations, include a revision in the protocol for Hb readings to be made at baseline or soon thereafter and also at Day 14 to capture essential data to address the issue of PADH, which is a signal that has been raised in association with Inj AS use.

This study has provided additional information on the safety of Inj AS to that given in the pivotal studies that led to the WHO recommendation for its use as the medicine of choice in severe malaria. The incidence and types of AEs and SAEs observed in this study validates the WHO recommendation.

CONCLUSION

The incidence of common AEs among patients treated with Inj AS in real-world settings was relatively low. The overall safety profile of Inj AS among the treatment cohort was favourable. An interventional study to address PADH would be useful. Future studies should consider larger cohort to document rare AEs as well.

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Site Manager: Patrick Buabeng (Agogo, Ghana). Advisor on Protocol and Study: Dr Stephan Duparc, Medicines for Malaria Venture.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest

H. Hilda Ampadu, Alexander N.O. Dodoo, Samuel Bosomprah, Helga Gardarsdottir, H.G.M. Leufkens, Dan Kajungu and Kwaku Poku Asante have no conflicts of interest. Samantha Akakpo and Pierre Hugo are full-time employees of Medicines for Malaria Venture (MMV).

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Ethical approval

The study received ethical approval from the Ghana Health Service Ethics Review Committee and the Uganda National Council for Science and Technology (UNCST). It was also registered on ClinicalTrials.gov with the ClinicalTrials.gov identifier NCT02817919. The study was conducted under Good Clinical Practice (GCP) guidelines taking into consideration the Declaration of Helsinki (as amended in October 2013) and local rules and regulations of participating countries and health facilities. All personnel involved in the study undertook and successfully passed an online GCP course prior to study initiation unless they already had a valid GCP certificate.

Patient consent

Written informed consent was obtained from the patients for publication of this study. A copy of the written consent may be requested for review from the corresponding author.

Consent for publication

Consent for publication was obtained as part of the informed consent process.

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CHAPTER 4.2

PRESCRIBING PATTERNS IN THE MANAGEMENT OF SEVERE MALARIA IN AFRICA AND THEIR COMPLIANCE WITH WHO RECOMMENDATIONS: A MODIFIED COHORT EVENT MONITORING STUDY IN PUBLIC HEALTH FACILITIES IN GHANA AND UGANDA

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Submitted

ABSTRACT

Background

Injectable Artesunate (Inj AS) is the World Health Organisation (WHO) first line recommended medication for the treatment of severe malaria to be followed with an oral artemisinin-combination therapy (ACT). There are few studies indicating how physicians prescribe Inj AS and ACTs for patients with severe malaria. This study was undertaken to evaluate prescription compliance to the WHO recommendation in 8 public health facilities in Ghana and Uganda. This was a modified cohort event monitoring study involving patients who were administered with antimalarial for treatment of presumed severe malaria. Patients prescribed at least one dose of injectable artesunate, artemether or quinine qualified to enrol in the study.

Methods

Patients were recruited at inpatient facilities and followed up by phone, at home or in hospital. Per WHO recommendation patients are to be prescribed 3 doses of Injectable Artesunate for at least 24 hours followed with ACT. We estimated compliance rate and presented 95% confidence interval. Log-binomial regression model was used to identify predictors for compliance. Based on the literature and limitations of available data from the patients' record, we considered diagnosis results, age, sex, weight, and country as potential predictors.

Results

A total of 1,191 patients completed the study, of which 93% were prescribed inj. Artesunate, 3.1% (Inj. Arthemeter or Quinine), 32.5% (Artemisinin combination therapy), and 26% (antibiotics). 391 (32.8%) were in Ghana and 800 (67.2%) were in Uganda. There were 582 (48.9%) females. The median age was 3.9 years (IQR=2, 9) and median weight was 13 kg (IQR=10, 20). Of the 1,191 patients, 329 of the prescriptions complied with WHO recommendation for treatment of severe malaria (compliance rate =27.6%; 95%CI=[25.2, 30.2]). Children under five years (Adjusted prevalence ratio (aPR)=1.20; 95%=[1.06, 1.36]; p=0.005), and Ghanaian setting (aPR=20.23; 95%CI=[13.86, 29.51]; p<0.0001) were identified as factors independently associated with increased compliance.

Conclusions

Inj AS is the most commonly prescribed medicine in the management of severe malaria in Ghana and Uganda. However, adherence to the WHO recommendation for at least 3 doses followed by a full course of ACT is low. Compliance was higher among children under five years possibly because they are high risk.

Keywords

Prescription, Malaria, Injectable Artesunate

INTRODUCTION

Over the past 10 years, there has been a huge decline in malaria cases as well as deaths from malaria. According to the World Malaria Report of the World Health Organisation (WHO), there has been an 18% reduction in malaria cases between 2010 and 2016 (1) accompanied by a huge decline in malaria deaths ranging from 27% in the Americas through 37% in Africa to 44% in South-East Asia. In spite of these huge reductions, the world witnessed 445,000 deaths due to malaria in 2016, which was the same as the year before with 91% of these deaths occurring in Africa. This shows that progress has reduced compared to the previous year. The vast majority of these estimated malaria deaths occurred in sub Saharan Africa. Global efforts set out in the Global Technical Strategy (GTS) for Malaria (2) as well as the Roll Back Malaria advocacy plan "Action and investment to defeat malaria" (3) aim to reduce malaria morbidity and mortality by at least 90% by 2030 compared to a 2015 baseline to meet the Sustainable Development Goals, especially SDG 3.3 (ending the epidemics of AIDS, tuberculosis, malaria and …) and SDG 3.8 (achieving universal health coverage ….. and access to safe, effective, quality and affordable essential medicines and vaccines) (4). Most malaria deaths are attributed to infections by *Plasmodium falciparum*. Poorly managed *P. falciparum* infections can lead to severe malaria which is associated with extremely high case fatality rates averaging 16-20% though extreme ranges as low as 2% and high as 100% have also been reported (5).

The WHO recommended product for severe malaria is the appropriate use of injectable artesunate (6). This recommendation is backed by a strong body of evidence including the landmark SEAQUAMAT (7) and AQUAMAT (8) studies as well as a Cochrane review (9). When injectable artesunate is not available, parenteral artemether or quinine are recommended. When used correctly, injectable artesunate, artemether or quinine are highly efficacious. The WHO also recommends that the parenteral medication is followed by a full course of oral artemisinin-combination therapy (ACT) to complete the treatment for severe malaria. However, there is little evidence of adherence to these recommendations in routine practice. In a study in Swaziland covering the period 2011-2015, where patients were diagnosed either by rapid diagnostic tests (RDTs), microscopy or both (10) less than half of those with severe malaria received injectable antimalarial and an oral course of ACT. Fourteen percent of the 1981 patients who had severe malaria were treated with artemether-lumefanthrine alone (11%) an ACT meant for treating uncomplicated malaria and not severe malaria. The rest were treated either with quinine alone (44%) or a combination of quinine and artemether-lumefanthrine (45%), i.e. an injectable antimalarial and an ACT. A cross-sectional survey of inpatient malaria investigation involving 13,014 children admitted to 5 hospitals in Western Kenya between 2014 and 2016 revealed high rates of presumptive treatment and possible over-use of injectable antimalarials (11). Another study in rural Western Kenya in 2013 showed poor knowledge and incorrect prescribing in the treatment of malaria in pregnancy (12). In view of the high

case fatality rate associated with severe malaria, it is important to understand the routine management of patients with severe malaria and to assess whether prescribing patterns are in line with recommended guidelines. The focus of this manuscript is on prescribers' compliance to the WHO recommendations for treating patients with severe malaria especially considering the paucity of publications on prescription adherence to recommended treatment for severe malaria.

In this study, we sought to examine medicine prescription in these settings regarding WHO guidance on the treatment of severe malaria to find out the level of compliance to the recommendations. We also examined factors independently associated with compliance to the WHO recommendation. Our findings provide insight into what pertains in real-world settings in relation to WHO guidance on treatment of severe malaria in particular in the use of the WHO recommended approach of prescribing injectable antimalalarials (artesunate, aremether or quinine) followed by a full course of oral ACT for the treatment of severe malaria.

METHOD

Study design and participants

This was a modified cohort event monitoring study involving patients who were prescribed injectable antimalarial for treatment of presumed severe malaria in 8 sites (4 each in Ghana and Uganda) between May and December 2016. The full details of the methods have been previously published (13). In short, eligible patients being treated for presumed severe malaria were recruited following signed informed consent. Data on medicine prescription were extracted from patients' records kept in paper "folders" in each health facility together with physician clerking notes, nurses' medicines administration records and pharmacy medicine supply details. Since the criteria for enrolment in this study was the prescription of injectable artesunate, artemether or quinine, all patients in the study had at least one dose of these medicines prescribed in addition to any concomitant medications prescribed. We also extracted data from the patient medical files on method of diagnosis, diagnosis or test results, date of treatment, age, sex, dose and frequency of antimalarial as well as the prescribed route of administration.

Sample size calculation

The sample size calculation was based on the primary outcome of compliance to WHO recommendation for treatment of severe malaria. The main analysis estimated the compliance rate and its 95% confidence. Therefore, the sample size was estimated using precision approach for one proportion in PASS 16 (NCSS, LLC, Kaysville, Utah, USA). We assumed that the compliance rate in the sample was 27%. Therefore, a sample size of 1212 produces a two-sided 95% confidence interval with a margin

of error equal to +/-2.5% (equivalent to a 2-sided confidence interval width equal to 0.050) when the sample proportion is 0.27.

Data management

Data on patient demography, the method used to test for malaria parasitaemia as part of the diagnosis of severe malaria as well as the overall management of the severe malaria episode itself were extracted from the patient records contained in paper "patient folders" in each facility. All these data were then transcribed onto the study Case Report Forms (CRFs). There were individual CRFs for collecting Demography, Medical History, Study and Concomitant Medication data, Laboratory data, the various Follow-Up information as well as individual CRFs for collecting Adverse Drug Reactions and Serious Adverse Drug Reactions data. All these CRFs formed what was called a CRF book per patient. Upon completion of a patient CRF book, the Site Coordinator as well as the Principal Investigator signed off on the book indicating that the book is complete. Data were entered, managed and stored in a specially created version of MedSpina™, an in-house electronic health records system that allows clinicians and other health workers to collect patients' data, including laboratory results, to facilitate patient care. The Data manager performed first pass quality control on all data points per patient CRF book by making sure data on the CRF matched the data in the database. All discrepant data points were queried for clarification/correction. Upon completion of the data management process, all data points for all patients were extracted for statistical analysis.

Outcome

The primary outcome was compliance to the WHO recommended treatment guidelines for severe malaria defined as the fraction of patient prescription that met WHO recommendation on treatment of severe malaria. The WHO guidelines specify that "Antimalarial drugs should be given parenterally for a minimum of 24 hours and replaced by oral medication as soon as it can be tolerated" For Inj AS, AR or Quinine the WHO guidance means that patients diagnosed with severe malaria should be treated with at least 3 doses of injectable antimalarial for at least 24 hours and should complete treatment with three days of an oral ACT.

Covariates and concomitant medication

Based on the literature and limitations of available data from the patients' record, we considered diagnosis results, age, sex, weight, and country as potential predictors of prescription. Use of concomitant medications was defined as any other medicines taken in addition to the WHO recommended antimalarials. Thus medicines being taken by patients during the course of the study such as antibiotics, haematinics, and analgesics among others was considered as covariates.

Statistical analysis

We re-coded the prescribed medicines into seven categories namely: injectable AS, artemether or quinine, ACT, antibiotics, analgesic or antipyretic, haematinic or vitamin, and others. We calculated the primary outcome as the number of patient prescriptions that met the WHO recommendation for treatment of severe malaria divided by the total number of patients who completed the study by end of follow up.

We used log binomial regression model to identify factors independently associated with compliance to the WHO recommendation. To construct a parsimonious model using all the potential predictors, we started by fitting a model for each potential predictor. In this model, each variable were candidates for inclusion in the full model if the p-value for association with prescription was 0.2 or less when considered individually. Variables were then removed from the model if the p-value for the likelihood ratio test was more than 0.2, provided removal did not change coefficients of variables in the model by more than 10%. Standard errors were adjusted for clustering of patients within health facilities. We assumed that missingness in the potential predictors were at random and not related to the outcome and therefore were not imputed. In a secondary analysis, we estimated the proportion of patients who were diagnosed with different malaria diagnostic methods. All analyses were performed using Stata 15 MP (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics of patients

A total of 1,262 patients were screened but 46 declined to participate giving 1,216 patients treated with AS and or other antimalarials and 25 having been lost to follow up leaving 1191 patients who were included in the analysis. Of the 1,191 remaining patients treated with injectable AS, AR, or Q and completed the study, 391 (32.8%) were in Ghana and 800 (67.2%) were in Uganda, there were 582 (48.9%) females; the median age was 3.9 years (IQR=2, 9) and median weight was 13 kg (IQR=10, 20) (Table 1).

Medicine prescription

Ninety three percent (93%) of the patients were prescribed inj. Artesunate, 3.1% (Inj. Arthemeter or Quinine), and 32.5% (oral Artemisinin combination therapy) (Figure 1). About a third (26%) of the patients were prescribed antibiotics (Figure 1). Of the 1,191 patients treated with AS, AR, or Q, 329 (27.6%; 95%CI: 25.2-30.2) of the prescriptions complied with WHO recommendation for treatment of severe malaria (Table 1). Compliance rate among children under five years was higher than that of children above five years of age (31.9% (CI; 28.6-35.4) vs. 21.2% (CI: 17.8-25.1) (Table 1). Majority of Ugandan patients were prescribed 3 doses of inj. AS, however this was largely not followed with co-prescription of oral ACT (Table 1).

Table 1. Proportion of patient prescription that complied with WHO recommendation by background characteristics

Characteristics	Number of patients (% of total)	Prescription of inj. AS in doses; n (%)			Co-prescription of ACT n (%)	# (%) of prescriptions that complied with WHO recommendation* n (%); [95%CI]
		< 3 doses	3 doses	>3 doses		
Sex						
Female	582 (48.9)	41 (7.0)	492 (84.5)	49 (8.4)	178 (30.6)	153 (26.3); [22.9, 30.0]
Male	609 (51.1)	43 (7.1)	526 (86.4)	40 (6.6)	196 (32.2)	176 (28.9); [25.4, 32.6]
Age (Years)						
Median (IQR)	3.9 (2, 9)					
5+	476 (40.0)	33 (6.9)	386 (81.9)	57 (12.0)	119 (25.0)	101 (21.2); [17.8, 25.1]
Under 5	712 (59.7)	50 (7.0)	630 (88.5)	32 (4.5)	254 (35.7)	227 (31.9); [28.6, 35.4]
Missing	3 (0.3)	1 (33.3)	2 (66.7)	0 (0)	1 (33.3)	
Weight (Kg)						
Median (IQR)	13 (10, 20)					
<10	276 (23.2)	19 (6.9)	246 (89.1)	11 (4.0)	89 (32.3)	85 (30.8); [25.6, 36.5]
10-19	510 (42.8)	35 (6.9)	450 (88.2)	25 (4.9)	191 (37.5)	163 (32.0); [28.0, 36.1]
20-29	111 (9.3)	8 (7.2)	96 (86.5)	7 (6.3)	32 (28.8)	29 (26.1); [18.8, 35.1]
30+	200 (16.8)	14 (7.0)	149 (74.5)	37 (18.5)	23 (11.5)	16 (8.0); [4.9, 12.7]
Missing	94 (7.9)	8 (8.5)	77 (81.9)	9 (9.6)	39 (41.5)	
Country						
Ghana	391 (32.8)	31 (7.9)	355 (90.8)	5 (1.3)	336 (85.9)	301 (77.0); [72.3, 80.9]
Uganda	800 (67.2)	53 (6.6)	663 (82.9)	84 (10.5)	38 (4.8)	28 (3.5); [2.4, 5.0]
Total	**1,191 (100)**	**84 (7.1)**	**1018 (85.5)**	**89 (7.5)**	**374 (31.4)**	**329 (27.6); [25.2, 30.2]**

*Compliance was defined as prescription of 3 doses of inj. AS within 24 hours and treatment with ACT.

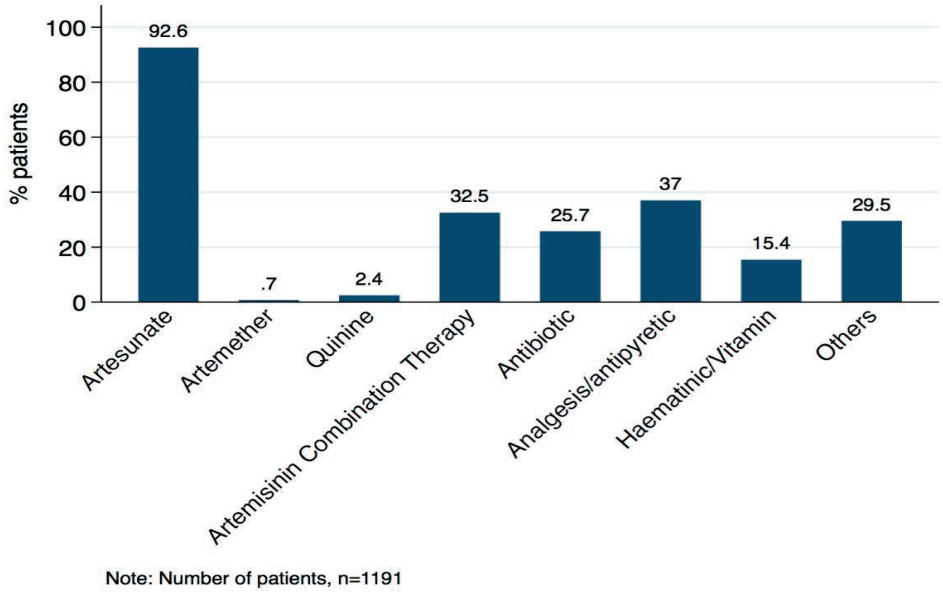

Figure 1. Types of medicines prescribed to patients with severe malaria

Overall, 374 of the patients (31.4%) had injectable antimalarial (Inj. AS or AR or Q) and co-prescription of ACT (Table 1). While about one-third (254/712) of children under five years had Inj antimalarial plus co-prescription of ACT, only 4.8% of patients in Uganda had injectable antimalarial (all of them Inj. AS) plus co-prescription of oral ACT (Table 1). 1,018 (85.5%) of the patients had 3 doses of inj. AS (Table 1).

Factors independently associated with compliance of patient with WHO recommendation

In univariable analyses, compliance to prescription of patients diagnosed as negative was about 4 times that among those diagnosed as positive whereas compliance to prescription to patients under 5 years of age was about 50% higher compared to children above 5 years (Table 2). Regarding weight, compliance to prescription among heavier patients was lower than that among lighter patients. There was no evidence that sex has any association with compliance (Table 2). In multivariable analysis where all factors have been adjusted for, the association of diagnostic results (Adjusted prevalence ratio (aPR)=4.56; 95%=[3.42, 6.08]; p<0.0001) and weight (20+kg vs. <10kg: aPR=0.65; 95%=[0.44, 0.96]; p=0.015) with compliance remained statistically significant at 5% level of significance (Table 2).

Diagnosis of severe malaria

Of the 1,191 patients, 569 (47.8%) were tested for parasitaemia using microscopy only whereas 353 (29.6%) were tested using RDT only. For each setting, 56.8% (222/391) of

patients in Ghana were tested using microscopy only compared to 43.4% (347/800) in Uganda whereas 16.6% (65/391) of the Ghanaian cohort were tested using RDT only compared to 36.0% (288/800) in Uganda (Figure 2). About 19.4% of patients in Ghana were tested using both RDT and Microscopy compared to 0.4% in Uganda (Figure 2).

Table 2. Factors independently associated with compliance of patient prescription with WHO recommendation (n=1,094)

Factors	Crude PR[95%CI]	LR p-value	Adjusted PR[95%CI]	LR p-value
Diagnosis result				
Positive	ref	<0.0001	Ref	<0.0001
Negative	4.16 [3.20, 5.41]		4.56 [3.42, 6.08]	
Sex				
Female	ref	0.314		
Male	1.10 [0.91, 1.32]			
Age (Years)				
5+	ref	<0.0001	Ref	0.205
Under 5	1.50 [1.23, 1.84]		1.16 [0.89, 1.51]	
Weight (Kg)				
<10	ref	<0.0001	Ref	0.015
10-19	1.03 [0.83, 1.29]		1.08 [0.88, 1.32]	
20+	0.47 [0.34, 0.65]		0.65 [0.44, 0.96]	

PR=prevalence ratio

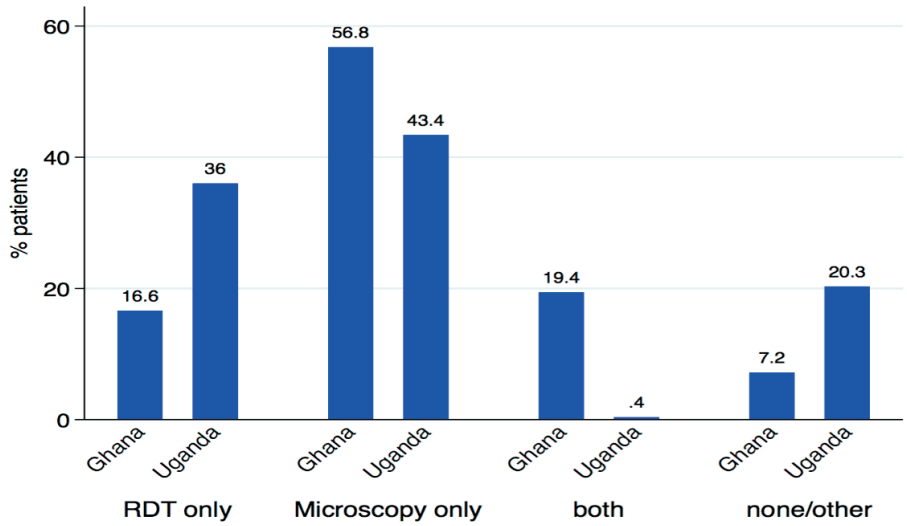

Figure 2. Proportion of patients diagnosed with different malaria diagnostic methods

DISCUSSION

This study reveals prescribers' prescription practices for patients treated for suspected severe malaria in 8 public health facilities in Ghana and Uganda. There was a very high level of prescription of Inj AS with 93% of the 1191 patients being prescribed the product. The rest were prescribed injectable quinine or artemether. Whilst 85.5% of the patients were prescribed 3 doses of Inj AS, only 31.4% had prescriptions for Inj AS followed by oral ACT. This shows a rather low level of compliance to the WHO recommendations for treating severe malaria which recommends the use of an injectable antimalarial for 24 hours (which equates to at least 3 doses of Injectable artesunate, quinine or artemether) followed by an oral ACT. There was high differences between countries with compliance being 20 times higher in Ghana compared to Uganda where only 4.8% of patients had a prescription for an injectable antimalarial followed by a co-prescription of an oral ACT. This finding contrasts with that of Achan et al. (14) where 429 out of 823 patients who received parenteral antimalarial also received oral medication. Even though there is a possibility that some patients may have received prescriptions for oral medications which were not captured in their in-patient folders and were also not reported to the study team for inclusion in the CRFs, it is extremely doubtful that this is frequent enough to reflect in the low follow-on ACTs prescribed. The very high prescription of Inj AS, the WHO recommended treatment, across the public health facilities in the 2 countries indicates its acceptance as the gold standard for treating severe malaria. However, there is the need to improve education to ensure that the "at least 24-hour parenteral treatment" is followed by a full course of oral ACT. Previous authors have shown poor practices in relation to the management of severe malaria. A 2009 severe malaria case study in Uganda concluded that management of severe malaria was poor with the correct drug at the time (quinine) being prescribed but used either mixed incorrectly or dosed sub-optimally (14). The authors concluded that only 16.9% of the 868 patients were appropriately treated for severe malaria.

In our study, prescribers appeared to pay particular attention to children under five years in respect of compliance with the WHO recommendations. Our findings showed a 20% increase in compliance among prescribers in relation to children under five years of age compared to older patients, suggesting a predilection towards more careful management of these children considered as high risk group. Although not statistically significant at 5% level in our study, compliance when prescribing for those who were negative for malaria parasites was about 15% higher than those positive for malaria parasites. Prescribing antimalarials for patients with parasitaemia is well known, both for severe as well as uncomplicated malaria and one study in Kenya in 2016, 69% of patients with negative malaria tests were still given parenteral treatment (11). An earlier study in Uganda from 2011 – 2013 involving 58095 children revealed similar practices (15). The WHO treatment guidelines advises prescribers not to withhold

antimalarial treatment from patients whilst waiting for parasitological confirmation of malaria even though it advises prescribers to look for other potential causes of the admission. Patients were prescribed antimalarials even when parasitological tests for malaria were negative. Prescribers tend to err on the side of caution to offer treatment even when malaria tests are negative though several studies have shown that withholding treatment in cases where malaria tests are negative is safe (16, 17). A reason for prescribing antimalarials for patients who tested negative for malaria may be that the attending physicians may want to treat for severe malaria in the absence of any other obvious clinical diagnosis. In patients with no malaria parasites, the treating physicians seeing no obvious cause for the clinical state rather appears to rigorously follow the WHO guidelines for treating severe malaria whilst also exploring treatment for other conditions which may be co-existing. In fact, the WHO guidelines for treating severe malaria highlights the similarities and co-existence of severe malaria, pneumonia and septicaemia and recommends simultaneous treatment for all these even before laboratory results are obtained. This may also explain the relatively high (26%) concomitant prescription of antibiotics in this study. Studies on drug utilisation in uncomplicated malaria (18) have shown similar results with co-prescription of antibiotics being high among patients with febrile illness.

The main medicines co-prescribed with the antimalarial treatments were analgesics (37%), antibiotics (26%) and haematinics (15%). Analgesics and haematinics are routinely prescribed for both uncomplicated and severe malaria to treat fever and anaemia respectively. As explained above, the use of antibiotics may be justified by the fact that attending physicians may be treating for other conditions which may be co-existing with the severe malaria. The drug prescription pattern in this study can be compared with those of a similar study on prescribing for patients with uncomplicated malaria where 31% and 26% received antibiotics and vitamins respectively (18). Such prescribing may be pragmatic in the treatment of severely ill patients in settings where diagnostics may also not be readily available and where the attending physicians has to quickly manage all probable causes of the severe illness whilst waiting for definite laboratory confirmation. A study in Malawi in 2012 on adherence to national guidelines for managing severe malaria highlighted some of the practical issues facing prescribers in the management of severely ill patients and noted that initiation of appropriate treatment depends on availability of adequate resources (19).

In relation to testing for malaria itself, 71.8% of the patients in Ghana were tested using RDT or microscopy with a further 19.7% being tested with both RDT and microscopy. Just under 80% of the patients in Uganda were tested for presence of malaria parasites using either RDT or microscopy with less than 1% being tested using both RDT and microscopy. Nearly 20% of patients in Uganda and 10% of patients in Ghana were diagnosed clinically without parasitological confirmation by the use of RDT or microscopy. The WHO guidelines for the treatment of malaria (3rd Edition) as

well as the practical handbook for Severe Malaria Management (3rd Edition, 2013) recommend the use of microscopy as part of the procedure for the diagnosis of severe malaria with a further recommendation that microscopy should be undertaken every 12 hours during the 2-3 days of parenteral treatment to monitor response. None of the patients had 12 hours microscopy to monitor treatment response.

Limitations of this study include the fact that the findings relate to prescriptions for patients in in-patient settings with no evidence that patients had been administered these medicines. Patients whose medications may be changed due to other considerations are still included in the analysis. Prescriptions that patients may already have but are unrelated to the current episode and admission may be missed. A drug utilisation study which examines availability of medicines in the treating facility as well as drug administration and its appropriateness in relation to age, weight and dose will be very helpful. In addition, the inclusion criteria for patients in this study was the prescription of parenteral antimalarials (injectable artesunate, artemether or quinine) for treating presumed or confirmed severe malaria even though it may just represent overuse of injectable antimalarials as found in previous studies. Further, this study did not look at provider related factors such as training on guidelines and health system related factors such as drug stock-outs which may influence the prescription patterns.

Conclusion

Inj AS is the most commonly prescribed medicine in the management of severe malaria in Ghana and Uganda. However, adherence to the WHO recommendation which recommends the prescribing of injectable antimalarial for at least 24 hours followed by a full course of oral ACT is low.

List of abbreviations

ACT: Artemisinin-Combination Therapy
AIDS: Acquired immunodeficiency Syndrome
AQUAMAT: African Quinine Artesunate Malaria Trial
AS : Injectable Artesunate ADR
CRF: Case Report Form
RDT: Rapid Diagnostic Test
SDG: Sustainable Development Goals
SEAQUAMAT: South East Asian Quinine Artesunate Malaria Trial
WHO: World Health Organisation

DECLARATIONS

Ethical approval

The study received ethical approval from the Ghana Health Service Ethics Review Committee and the Uganda National Council for Science and Technology (UNCST). It was also registered on ClinicalTrials.gov with the ClinicalTrials.gov identifier NCT02817919. The study was conducted under Good Clinical Practice (GCP) guidelines taking into consideration the Declaration of Helsinki (as amended in October 2013) and local rules and regulations of participating countries and health facilities. All personnel involved in the study undertook and successfully passed an online GCP course prior to study initiation unless they already had a valid GCP certificate.

Patient consent

Written informed consent was obtained from the patients for publication of this study. A copy of the written consent may be requested for review from the corresponding author.

Consent for publication

Consent for publication was obtained as part of the informed consent process.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

All authors declare that they have no competing interests.

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Authors' Contribution

ANOD, HHA and KP conceived and designed the study. HHA, SB and DK conducted the data collection and analysis. HHA supervised the study. ANOD, KP and PH contributed to interpretation of the results and writing of the manuscript. KP and ANOD were actively involved in the study progress and revised the manuscript critically. HGML, HG, DK, SA and PH were also involved in reviewing and revising of the manuscript. All authors approved the final version of the manuscript.

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CHAPTER 5

GENERAL DISCUSSION

INTRODUCTION

In this thesis we aimed to provide insight into the emergence and growth of national pharmacovigilance systems in African countries. The 21st century has seen rapid development of pharmacovigilance activities in Africa. An increased number of countries have established national pharmacovigilance systems mostly supporting passive surveillance based on the governance structure of the WHO Programme for International Drug Monitoring (PIDM). However, development beyond passive surveillance (spontaneous reporting) has been challenging (1), (2), (3) due to fragmentation of the system and difficulties in acquiring resources, building capacity and critical infrastructure. In drafting recommendations to overcome these challenges (1), (2), (3), various authors have stressed the need to develop context specific approaches that take into consideration the resource limitations, local health needs of population groups, characteristics of the healthcare systems and socio-economic dynamics endemic to the African settings. The thesis studies these context-specific approaches by focusing on the role and position of national pharmacovigilance centres, the participation and awareness of reporters and evaluators of Adverse Drug Reactions (ADR) in African countries and the feasibility of generating evidence on safety and use of medicines in African clinical practice.

THE ROLE AND POSITION OF NATIONAL PHARMACOVIGILANCE CENTRES

Chapter 2.1 characterised Individual Case Safety Reports (ICSR) reporting activities in Africa and compared ICSRs reported by national centres in Africa with those reported by the rest of the world. We found an increase in the number of African countries that have joined the PIDM (from 2 in 1992 to 32 in 2015). Reporting of ICSR to has also grown (four fold increase) from 25,000 ADRs in 2010 (3) to 103,499 in 2015 (Chapter 2.1). Despite this increase, we showed that reporting from African countries still only contributes less than 1 % of the ADRs that have been submitted to VigiBase® which is very low considering that more than one in seven of the world's citizens are living in African countries. The ADR reports submitted are mainly for products for infectious diseases such as HIV, reflecting the disease burden on the African continent. However, when comparing with reporting from the rest of the world we found that the proportion of ADRs submitted for main product classes treating HIV/AIDS (nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors and combination antivirals), was three to six fold higher for the rest of the world than for African countries. We also found a relatively high number of reports to Angiotensin-Converting Enzyme (ACE) inhibitors in African ADRs compared to the rest of the world (2.42% vs. 1.32%).) This finding confirms prior findings by Berhe et al (4), which examined ADRs to cardiometabolic drugs and found a disproportionately higher reporting of ADRs to ACE inhibitors when comparing ADRs from Africa with

the rest of the world (36 % vs.14 %). This may confirm the changing morbidity patterns on the continent with a steeply increasing burden of communicable diseases, in addition to the persisting dominance of non-communicable diseases (5). The ongoing developments and improvements of the pharmacovigilance systems in Africa are likely to stimulate further growth in the reporting and submission of ICSRs of good quality to VigiBase®.

In Chapter 2.2 we provided a broader view on the functioning of national pharmacovigilance centres in African countries by examining the resources, relationships and organisational capacity of national centres. We found that strategic leaders of national centres often attributed success of their pharmacovigilance activities to political (e.g. legal mandate) and technical (e.g. building critical infrastructure) achievements, while unsuccessful activities were often attributed to a lack of financial and human resources. Our study revealed three core challenges national centres need to overcome in order to become the central coordinating bodies of their national pharmacovigilance systems: over-reliance on development partners for key resources, seeming indifference of national governments to support these centres and unsustainable engagement with Public Health Programmes (PHPs). Limited key resources, such as financial and human resources which hampers the functioning of national centres have been identified by others (1), (2), (6). Our research specifies these findings by showing that in the search for key resources national centres have become dependent on development partners for resources. Previous authors identified the lack of political will and commitment from national governments in Africa for pharmacovigilance (3). Our research substantiates this finding by showing that national governments tend to give national centres political and technical resources to gain membership into the PIDM but commitments beyond that are not guaranteed. Collaboration of national centres with PHPs is key for the reporting function of the pharmacovigilance system, as PHPs are able to collect safety data on a regular basis compared to routine clinical practice (7), (8). Our research revealed that sustainable engagement with PHPs is difficult to realise although a few national centres have been able to build mutually beneficial trust-based relationships with PHPs which has been instrumental in their safety monitoring efforts.

PARTICIPATION AND AWARENESS OF REPORTERS AND EVALUATORS

Awareness of different stakeholders, such as patients and HCPs, of the importance of pharmacovigilance contributes to increase reporting of ADRs (9), (10), (11). We assessed the awareness of Ghanaian patients about ADRs and ADR reporting (Chapter 3.1) which revealed that of the 491 participants included in our study, 38% had experienced an ADR, of which 67% reported the ADR to someone, 68% of them reported it to a doctor. However, only 3% of the 491 participants in our study were

aware of the Ghana-Food and Drug Authority's patient reporting system. Our study results are similar to Sabblah et al (12) in terms of awareness of ADRs but differ on the awareness of ADR reporting channels. Sabblah et al reported that approximately half of the respondents (49.5%) from their study were aware and able to report ADRs directly to the Ghana-Food and Drug Authority's patient reporting system. The differences might relate to different sample size and settings included in these two studies, as the study by Sabblah et al only included patients from two community pharmacies and our study included patients from twenty eight different health care facilities including government hospital pharmacies, private hospital pharmacies, community pharmacies and licensed over-the-counter medicine sellers.

It is important to fulfil the decision making function of a pharmacovigilance system with data collected in Africa in order to improve the chances of detecting any African-specific safety issues and to make informed decisions about local drug use policies. Only a few studies in Africa have attempted to provide local data to justify local drug use policy, specifically in the context of PHPs. These include studies on the safety of post-exposure prophylaxis with anti-retroviral (13) or the influence of modification of anti-retroviral therapy on the ADRs experienced by patients (14). However in Chapter 3.2 we showed that so far no major drug safety policy decisions have been taken by PHPs that are based on data collected in Africa. Data from Africa seem to have contributed little to the safety signals raised in relation to antiretroviral products. For instance, abacavir hypersensitivity have been more and better described in studies from developed countries than from Africa which has the highest disease burden (15). Further, the risks of myocardial infarction with nelfinavir, anaemia with zidovudine, rashes with nevirapine and lactic acidosis with stavudine have all been identified from clinical trials and post-approval studies in countries outside Africa (15). This finding is surprising given that it can be reasonably expected that the necessary safety data has been collected particularly within well-funded PHPs in Africa.

GENERATING EVIDENCE ON SAFETY AND USE OF MEDICINES IN CLINICAL PRACTICE

Spontaneous reporting schemes alone cannot yield the necessary data needed for decision making and should therefore be complemented with active pharmacovigilance methodologies that collect safety data in clinical practice. With the emergence of pharmacovigilance systems in Africa, development of active monitoring of products in African markets requires that fit-for-purpose and fit-for-context methods are used. In Chapter 4 an active surveillance methodology was tested to collect data in clinical practice (modified cohort event monitoring). The data collected was first used to assess the safety profile of injectable Artesunate (Inj AS) in public health facilities in countries where severe malaria is not always properly diagnosed (microscopy; rapid diagnostic tests; laboratory measurement of Hb) and facilities for safety monitoring

vary. Inj AS is the number one drug recommended by the WHO for the treatment of severe malaria. In Chapter 4.1 we applied a modified cohort event monitoring (mCEM) approach and found that the results obtained from our study are similar to the findings from the SEAQUAMAT and AQUAMAT clinical trials (16), (17). The overall incidence of AE was 17.9% (197/1103) which is similar to that listed in the public assessment reports (PARs; Part 4: Summary of Product Characteristics) for Inj AS, as published by the WHO (18). Our study findings provide validation for the safety profile of Inj AS as recorded in the PAR. Further, we found a lower number of deaths in our study than what was reported in the AQUAMAT and SEAQUAMAT trials. In the AQUAMAT study, 8.5% of the 2712 patients in the artesunate arm died, whilst 15% of the 730 patients in the artesunate arm of the SEAQUAMAT study died (17), (16) compared to our study which recorded an all-cause death rate of 1.2% (13/1103). This could partially be explained by different inclusion criteria (age and diagnosis criteria for severe malaria) between these clinical trials and our study. Our study also confirms that the mCEM can be used for context specific data collection in adherence to international standards, however future studies should consider larger cohorts that would allow for capturing rare adverse events. Other approaches that have been proven feasible are the quantitative signal detection, where databases of reports of adverse events following immunization produced data used to identify the most frequently occurring vaccine related safety issues (19). These examples (Chapter 4.1, (19)) underscore the feasibility of generating useful data in African pharmacovigilance systems based on appropriate context specific methodologies.

The WHO publishes treatment guidelines for various therapies to promote the safe and effective use of these therapies. Injectable artesunate is the first line therapy for treating malaria according to the WHO (20). Patients should be prescribed three doses of Injectable Artesunate, Quinine or Artemether within the first 24 hours followed with oral Artemisinin Combination Therapy (ACT) (20). In Chapter 4.2 the data collected through the cohort-event monitoring methodology was used to assess prescribing practices of African health care professionals and investigate if these are in line with the WHO treatment guidelines. We found that Inj AS is the most commonly prescribed medicine in the management of severe malaria in Ghana and Uganda. However, only 27.6% (329 out of 1191) of patients receive at least three doses if Inj AS followed by a full course of oral ACT. Compliance with WHO treatment recommendations was however about 50% higher when treating children under five compared to children above 5 years, possibly because they have a higher risk of dying from severe malaria. In line with other studies (21), (22) we found that prescribing of Inj AS in African countries deviates significantly from the WHO reference targets (three doses of Injectable Artesunate, Quinine or Artemether within the first 24 hours followed with oral Artemisinin Combination Therapy). Our study showed that active surveillance methodologies are not only useful to monitor safety of products but can

also be used to monitor prescription practices of health care professionals in clinical practice in low resource settings.

Implications for practice and recommendations for further academic research

This thesis revealed that most African countries have met the WHO minimum requirements for PDIM memberships and have national pharmacovigilance systems in place. However with pharmacovigilance activities expanding, various system elements and their inter-relationships need to be further strengthened. The findings from our research point to three areas were such strengthening is particularly important 1) building and organising sustainable relationships between national pharmacovigilance centres, national governments and external stakeholders, 2) strengthening the reporting function through increased awareness of ADRs and particularly ADR reporting channels and 3) strengthening reliance on context specific data for regulatory decision making.

Our research conducted in Chapter 2 revealed that a key consideration for national centres in evolving African national pharmacovigilance systems is how to build and organize sustainable relationships with national governments and external stakeholders such as donors. A number of aspects are particularly of relevance in building and managing such relationships. First, there are questions about how to coordinate the acquisition of resources by the national pharmacovigilance centre. One way is through centralized resource coordination by national governments where the national government act as the convener of resources for the pharmacovigilance system from all stakeholders. This approach may however only be feasible for countries with well-organised public administrative structures including a well-functioning Ministry of Health (23) as well as relatively advanced pharmacovigilance systems. Second, there are questions about the autonomy of national pharmacovigilance centres vis-à-vis the national government. It could be explored whether national pharmacovigilance centres in countries with advanced healthcare systems and structures for passive and active surveillance in place (23) can operate as autonomous or semi-autonomous organisations from the Ministry of Health as is common in pharmacovigilance systems in high income countries. With autonomy the national pharmacovigilance centres will be able to draw their own work plan and submit their budgets to the national government. The ability to acquire its own resources and the independence to utilise these resources to achieve outcomes, may reduce national centres reliance on a small number of stakeholders in the system. Third, there are questions about how to become independent from external stakeholders such as donors. Our research revealed that donors and national pharmacovigilance centres are not always aligning their pharmacovigilance activities leading to redundancy and duplication of efforts. It could be explored whether a pharmacovigilance

coordinator could coordinate activities between the two structures. Stemming from their documented lack of organisational capacity, national pharmacovigilance centres are not the central coordinating bodies of their system and currently most national pharmacovigilance centres in Africa mainly focus on collecting spontaneous reports. It is important to draft visions of how national pharmacovigilance centres could achieve a more coordinating role in their systems in the future.

Creating awareness on ADRs is important as revealed by our research in **Chapter 3**. In this thesis we found that particularly awareness of formal channels and accessibility of the channels is limited. A number of approaches can be adopted to increase awareness of the channels for ADR reporting. The first option is for national pharmacovigilance centres to continue their awareness campaigns to the general public. An emphasis on the benefits of ADR reporting and different routes to facilitate such reporting should form part of all awareness campaigns. The second option is to collaborate closely with HCPs to create awareness to patients. Explaining the benefits of ADR reporting to patients and encouraging them to report ADRs should form part of routine patient care by HCPs. This will be particularly important in donor funded pharmacovigilance programmes where HCPs encounter patients more often. The final option is for national pharmacovigilance centres to pay attention to patient's preferences for reporting ADRs. Here it is important for national pharmacovigilance centres not to settle on one dominant channel for ADR reporting but keep the pharmacovigilance system flexible and allow for different ways of reporting that are in line with patient's preferences. Routes of reporting such as via text messages, internet, mobile phone apps and reporting via different types of HCPs such as community pharmacy shop attendants can be explored depending on patient needs and geographical contexts. Our research in **Chapter 3** also revealed that patients will rather report ADRs to a doctor and specific prescribers yet in most countries in Africa the pharmacy is the first point of call for most patients (24). National pharmacovigilance centres or other system structures could educate patients and convince them to widen their preferences to include for example other HCPs such as pharmacist and pharmacy shop attendants as mentioned above. National pharmacovigilance centres should take these additional preferences into account when designing reporting channels and awareness campaigns.

Our findings in **Chapter 4** suggest that active surveillance methodologies can be used in low resource settings to collect context specific data for decision making. Stakeholders should consider these methods when the need arises to collect data on medicines that are used in Africa. Although we showed that this methodology is feasible for assessing safety of therapies for communicable diseases, active surveillance methodologies should also be tested for other scenarios such as new drug introductions, different types of therapies including those used to treat non-communicable diseases and larger patient populations. In addition, as data

infrastructures develop in Africa the feasibility of using Electronic Health Records (EHR) for safety monitoring systems should be explored. Not only can such a system assist in monitoring safety but it can also support physicians with prescribing decisions. Many EHRs contain an e-prescribing interface that provides information on the efficacy, side-effects and interaction information that can be used to assist physicians to prescribe medicines to patients in a safe and effective manner (25), (26). Another important question is if Africa should only rely on context specific data for decision making or only in case of specific medical products or medical products that are used in large volumes in African clinical practice.

Based on the conducted studies in this thesis we also recommend two avenues for further research on pharmacovigilance systems in Africa. A first avenue entails studies focused on the continuous evaluation of the pharmacovigilance system as it is constantly evolving to understand its impact on drug safety in Africa. While we have generated new and useful insights on the changing role and position of national pharmacovigilance centres, our studies did not reveal how this position facilitates or impedes the centre in its functioning and how it contributes to reducing medication-related problems. Our study could thus be extended to studying national centres outputs and outcomes in increasing drug safety. This could also contribute to finding appropriate governance structure for the centre's functioning in the system. Secondly, national pharmacovigilance centres are only one of the relevant structures within national pharmacovigilance systems. Future studies could focus on other structures and also more systematically study the relationships between the different structures in the system. For example both national government and national centres may need to consider how industry, as a key stakeholder will contribute resources (including financial resources) towards sustainable national pharmacovigilance systems in a way that is ethical and compliant with regulations. Thirdly, studying the impact of different types of regulations on enhanced reporting (output) and ensuring drug safety (outcome) is also essential. One could ask whether and to what extent stringent regulation (regarding evidence generation for safety and setting up post-marketing monitoring systems) of the pharmaceutical industry in Africa as pertains in developed countries could help augment the reporting function of the African pharmacovigilance system. For example it's been six years since the implementation of the Ghana QPPV law (27) which seems an appropriate moment to ascertain if ADR reporting in Ghana has improved. Fourthly, studying how pharmacovigilance systems evolve in different country-specific directions might provide insight in national differences in pharmacovigilance systems and better understanding of what works in which geographical context.

A second avenue for further research builds on the efforts in Chapter 4 to test application of active pharmacovigilance surveillance methodologies in Africa. As African healthcare systems develop, future approaches to generating context specific

data could include using EHR from administrative or health care databases to monitor drug utilization and safety (28). These databases could in future be expanded or linked with ADR form data interface that will enable pro-active ADR data collection. Evidence from a recent study in Ghana also shows that mobile phones are a feasible and a realistic approach for pharmacovigilance activities and provide robust data in prospective studies (29). Our research in **Chapter 4** explored one type of active data collection method, for a single communicable disease in a little over 1,000 patients. Future studies could include assessing the feasibility of applying active surveillance methods to collect data for different study designs such as interventional studies. They should also explore the applicability of such methods for generating data on safety of other types of therapies, including those for non-communicable diseases. For example postartesunate delayed haemolysis (PADH) is a safety issue that has been raised following identification of a number of delayed haemolysis cases after treatment with Inj AS (30), (31), (32) and our study reported two serious anaemia cases as well, hence an interventional study which measures haemoglobin at enrolment and throughout the follow up period to address PADH would be useful.

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CHAPTER 6

SUMMARY

CHAPTER 6.1

SUMMARY

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

Pharmacovigilance emerged as a regulatory activity in Africa in the early 1980s through a series of meetings between Health Care Professionals (HCPs) and national regulatory authorities. The goal of these meetings was to discuss on how to develop national pharmacovigilance systems within the context of the WHO Programme for International Drug Monitoring (PIDM). Until then, pharmacovigilance in Africa was mainly considered a public health activity conducted in universities or through professional doctors associations. Pharmacovigilance was not a regulatory activity backed by political legitimacy provided through laws, regulation and standards.

The PIDM provides a governance structure to support the conduct of pharmacovigilance activities. A first step in developing a national pharmacovigilance system according to this structure entails the establishment of a national pharmacovigilance centre, a national spontaneous reporting system and database, an advisory committee and a communication strategy. These are also requirements for becoming a member of the PIDM. The first African countries joined the PIDM between 1992 and 1998 (Morocco, South Africa, Tanzania, Tunisia and Zimbabwe). From 2000 to 2018, twenty eight other African countries joined the PIDM. The growth in PIDM membership indicates increased priority for pharmacovigilance in African countries and ongoing activities to develop national pharmacovigilance systems.

Most national pharmacovigilance systems in Africa have been developed as part of efforts to eradicate diseases that are on the WHO disease priority list such as HIV/AIDS, tuberculosis and malaria. The structure of these systems resembles the healthcare delivery systems in the respective countries. Functioning of the systems relies on development partners for support through Public Health Programmes (PHPs) also known as disease control programmes, there is limited contribution from large research-based pharmaceutical companies and there is a relatively high circulation of substandard and counterfeit medicines. All these factors suggest that national pharmacovigilance systems in Africa have unique structures and challenges and are evolving along different paths from those taken in more established pharmacovigilance systems.

Against this background, the thesis aimed to provide insight into the emergence and growth of national pharmacovigilance systems in African countries by looking at different elements of the national pharmacovigilance system. The thesis focused on examining the role and position of the national pharmacovigilance centre, the participation and awareness of reporters and evaluators and lastly, the feasibility of generating evidence on the safety and use of medicines in clinical practice in low resource settings in Africa.

The thesis is organised into five main chapters. **Chapter 1** is introductory and provides a general overview of the research topic and research objectives of the thesis as laid out above. The subsequent chapters are summarised as follows:

Chapter 2 examined the role and position of national pharmacovigilance centres in African pharmacovigilance systems. In **Chapter 2.1** we used the VigiBase® database of Adverse Drug Reactions (ADRs), to characterise ADRs reported by African countries and compared them to ADRs that are reported by the Rest of the World (RoW). At the end of September 2015, and African PIDM members had cumulatively submitted 103,499 Individual Case Safety Reports (0.88 % of global ADRs) to VigiBase®. The main class of products for which ADRs were reported by African countries differed from those reported by the RoW. These included nucleoside and nucleotide reverse transcriptase inhibitors (14.0 %), non-nucleoside reverse transcriptase inhibitors (9.1 %), antivirals for the treatment of HIV infections (5.5 %), combinations of sulfonamides and trimethoprim (3.0 %) and angiotensin-converting enzyme (ACE) inhibitors (2.4 %). The main system organ classes reported from Africa versus the RoW include skin and subcutaneous tissue disorders (31.1 % vs. 19.6 %), general disorders and administration site conditions (20.9 % vs. 30.5 %) and nervous system disorders (17.5 % vs. 19.1 %). The 18-44 years age group dominated ADR reporting from Africa, while the 45-64 years age group dominated ADR reporting from the RoW. Identical proportions of females (57.1% Africa and the RoW) and males (37.1 % Africa and the RoW) were represented. The results demonstrate that although the number of ADR reportsfrom Africa has increased substantially, ADR reports from Africa still make up <1 % of the global total in VigiBase®. Ongoing developments and improvements of the pharmacovigilance systems in Africa are likely to stimulate further growth in submission of ADR reports of good quality to VigiBase®.

Having determined that ADR reporting is limited in Africa, we examined the organisational capacity of national pharmacovigilance centres as one of the key organisations responsible for the reporting function of the pharmacovigilance system. In **Chapter 2.2** we provided insight into activities of national centres that were deemed successful or unsuccessful by their strategic leaders and by assessing whether the attribution of success or failure was associated with particular types of resources or relationships with stakeholders. We interviewed eighteen strategic leaders of national pharmacovigilance centres in Africa to ascertain what they deemed successful and unsuccessful pharmacovigilance activities of their centres. We found that strategic leaders most often attributed successful experiences to the acquisition of political (e.g. legal mandate) or technical (e.g. active surveillance database) resources, while unsuccessful experiences were most often attributed to the lack of financial and human resources. Stakeholders that were most often mentioned in association with successful experiences were national government and development partners, whereas national government and public health programmes (PHPs) were often mentioned in

unsuccessful experiences. Based on the interview analysis we conclude that national pharmacovigilance centres in Africa are faced with three core challenges: (1) over-reliance on development partners, (2) seeming indifference of national governments to provide support after national pharmacovigilance centres have gained membership of the PIDM, (3) engaging public health programmes in a sustainable way.

In order to increase reporting of ADRs to the national pharmacovigilance centre, it is important to make sure that the different stakeholders involved in pharmacovigilance are aware of their roles in the generation and use of drug safety data. Chapter 3 evaluated national pharmacovigilance systems from the perspective of reporters (patients) and evaluators (HCPs) and how they contribute to fulfilling pharmacovigilance system functions. In Chapter 3.1 we assessed the awareness of Ghanaian patients about ADRs and ADR reporting. This was a two-part study consisting of a survey to quantify the awareness of Ghanaian patients on ADRs and ADR-reporting, and in-depth interviews to explore how patients recognise an ADR and the steps they take thereafter. Participants were selected from 28 health care facilities (HCF) in rural and urban areas in 4 out of the 10 administrative regions of Ghana. Of the 491 participants included in our study, 38% had experienced an ADR, of which 67% reported the ADR to someone, 68% of them reported it to a doctor. Further, only 3% of the 491 participants were aware of the Ghana-Food and Drug Authority's patient reporting system. These findings suggest that there is a mismatch between the preferences of patients to report their ADRs to doctors and the first line of contact for Ghanaian patients which is the pharmacist/pharmacy attendants. Low awareness of the formal patient reporting system might have contributed to patients mainly citing personal benefit in reporting ADRs instead of communal benefits. Moreover we found that there are multiple other obstacles that hamper patient reporting of ADRs in Ghana such as poor dispensing practices and socio-economic differences between patients and HCPs which warrant further attention.

There is limited knowledge on the use of locally collected safety data for medicines decision making in Africa. Chapter 3.2 is therefore a literature review to assess the level to which pharmacovigilance decision making in the context of African PHPs has been driven by locally generated data, and to examine whether the underlying evidence has been obtained through traditional pharmacovigilance approaches or by the use of newer methods and tools. We showed that so far no major drug safety policy decisions have been taken by PHPs that are based on data collected in Africa. Data from Africa seem to have contributed little to the safety signals raised in relation to antiretroviral products. For instance, abacavir hypersensitivity reaction is better described in clinical trials from high-income countries than from Africa which has the highest HIV disease burden. Further, the risks of myocardial infarction with nelfinavir, anaemia with zidovudine, rashes with nevirapine and lactic acidosis with stavudine have all been identified from clinical trials and post-approval studies in

countries outside Africa. This finding is surprising given that it can be expected that the necessary safety data to support decisions about medicines safety has been collected particularly within well-funded PHPs in Africa.

Data on the use and safety of medicines originating from African clinical practice may be needed to make decisions that pertain to often used products in African countries. In **Chapter 4** we therefore assessed the feasibility of implementing an active method to collect data on use and safety of products in low resource settings in Africa. In **Chapter 4.1** we assessed if the active data collection methodology modified cohort event monitoring (mCEM) can be used to assess the safety profile of Injectable Artesunate (Inj AS) in clinical practice and in accordance with international guidelines. A total of 1103 eligible patients were administered Inj AS, of which 360 patients were in Ghana and 743 in Uganda. The incidence of any ADRs by the end of follow-up among patients treated with Inj AS was 17.9% (197/1103) (95% confidence interval [CI] 15.8-20.3). This is in line with what has been reported in clinical trials. The incidence of common ADRs among patients treated with Inj AS was found to be relatively low. The top five ADRs recorded among patients treated with Inj. AS being pyrexia (3.5%), abdominal pain (2.5%), diarrhoea (1.7%), cough (1.5%) and asthenia (1.5%). Most of these occurred in the first 14 days following treatment. The median time-to-onset of any ADR was 9 days (interquartile range (IQR) = 4, 14). Regarding the relatedness of these ADRs to Inj AS, 78.9% of pyrexia (30/38), 63.0% of abdominal pain (17/27), 68.4% of diarrhoea (13/19), 85.5% of cough (14/16) and 75.0% of asthenia (12/16) were assessed as 'possibly' related. There were 17 Serious Adverse Drug Reactions (SADRs) including 13 deaths. Two of the deaths were 'possibly' related to Inj AS, as were three non-fatal SADRs: severe abdominal pain, failure of therapy and severe anaemia. Our study provides a successful example of how mCEM can be used for context specific data collection conform international guidelines.

Non-adherence to treatment guidelines may expose patients to harm. The WHO publishes treatment guidelines for various therapies to promote the safe and effective use of these therapies. In **Chapter 4.2** we used active surveillance methodology to assess if physicians adhered to the WHO treatment guidelines when prescribing injectable antimalarials to treat patients with severe malaria. A total of 1,191 patients where included in the study, of which 93.0% were prescribed inj. Artesunate, 3.1% Inj. Arthemeter or Quinine, 32.5% Artemisinin Combination Therapy (ACT), and 26.1% antibiotics. Of included patients, 391 (32.8%) were in Ghana and 800 (67.2%) were in Uganda. There were 582 (48.9%) females. The median age was 3.9 years (IQR=2, 9) and median weight was 13 kg (IQR=10, 20). Of the 1,191 patients, 329 (27.6%, 95%CI=[25.2, 30.2]) of patients got injectable antimalarials that where prescribed according to WHO recommendation for treatment of severe malaria. Inj AS was the most commonly prescribed medicine in the management of severe malaria in Ghana and Uganda. However, adherence to the WHO treatment guidelines for at

least 3 doses followed by a full course of ACT is low. Compliance was higher for treatment of children under five years.

The various chapters in this thesis on the growth and emergence of national pharmacovigilance systems in African countries provide a broad perspective on the challenges facing African national pharmacovigilance systems. The conclusion and discussion in **Chapter 5** revealed that most African countries have met the WHO minimum requirements for PIDM memberships and have formal national pharmacovigilance systems in place. However with pharmacovigilance activities expanding, various system structures and relationships between system participants need to be further strengthened. The findings in the thesis point to three areas where such strengthening is particularly needed 1) building and organising sustainable relationships between national pharmacovigilance centres, national governments and other stakeholders, 2) strengthening the reporting function of the pharmacovigilance system through increased awareness of ADRs and by taking patient needs and practices into account in the design of ADR reporting channels and 3) strengthening reliance on context specific data for regulatory decision making. Based on the conducted studies in this thesis we also recommend two avenues for further research on pharmacovigilance systems in Africa. A first avenue focuses on continuous evaluation of the pharmacovigilance system as it is constantly evolving, paying particular attention to its impact on drug safety and public health in African countries. A second avenue builds on the efforts in **Chapter 4** to test the application of active surveillance methodologies in Africa. Future research could assess the feasibility of applying active surveillance methodologies to collect data for different study designs and therapies as well as paying attention to the use of newer technologies and tools for data collection such as mobile phones and electronic health record systems.

CHAPTER 6.2

SAMENVATTING

Farmacovigilantie is de wetenschap en activiteiten met betrekking tot de opsporing van, beoordeling van, het inzicht verkrijgen in, en voorkomen van bijwerkingen of een ander mogelijk probleem gerelateerd aan geneesmiddelen.

Farmacovigilantie ontstond in Afrika in de vroege jaren tachtig door middel van een serie van bijeenkomsten tussen beroepsbeoefenaars uit de gezondheidssector en regulatoire autoriteiten. Het doel van deze bijeenkomsten was om te discussiëren over het ontwikkelen van nationale farmacovigilantie systemen binnen het *Programme for International Drug Monitoring (PIDM)* van de Wereldgezondheidsorganisatie. Tot die tijd werd farmacovigilantie in Afrika voornamelijk gezien als een publieke gezondheidsactiviteit uitgevoerd op universiteiten en door artsenverenigingen. Farmacovigilantie was geen regulatoire activiteit ondersteund door politieke legitimiteit en wetten, regulering en standaarden.

Het PIDM biedt een bestuurlijke structuur om de uitvoering van farmacovigilantie activiteiten te ondersteunen. Een eerste stap in het ontwikkelen van een nationaal farmacovigilantie systeem conform deze structuur omvat het oprichten van een nationaal farmacovigilantie centrum, een nationaal systeem en database voor het melden van spontane bijwerkingen, een adviescommissie en een communicatiestrategie. Dit zijn ook de eisen om lid te worden van het PIDM. De eerste Afrikaanse landen werden lid van het PIDM tussen 1992 en 1998 (Marokko, Zuid Afrika, Tanzania, Tunesië en Zimbabwe). Vanaf 2000 tot 2018 volgden 28 andere Afrikaanse landen. De groei in het PIDM lidmaatschap is een indicatie van de toegenomen prioriteit voor farmacovigilantie in Afrikaanse landen en van doorlopende activiteiten om nationale farmacovigilantie systemen te ontwikkelen.

De meeste nationale farmacovigilantie systemen in Afrika zijn ontwikkeld als onderdeel van inspanningen om ziektes uit te bannen waaraan de Wereldgezondheidsorganisatie hoge prioriteit geeft zoals hiv/aids, tuberculose en malaria. De structuren van deze systemen lijken op die van de gezondheidszorgsystemen in de landen. Het functioneren van de systemen is afhankelijk van ondersteuning van publieke gezondheidszorg programma's door ontwikkelingsorganisaties; er is een beperkte bijdrage van grote onderzoeks-gebaseerde farmaceutische bedrijven aan het systeem en er is een grote circulatie van nagemaakte en lage kwaliteit geneesmiddelen. Dit suggereert dat nationale farmacovigilantie systemen in Afrika te maken hebben met unieke structuren en uitdagingen en zich zullen ontwikkelen langs andere paden dan die genomen in meer gevestigde farmacovigilantie systemen.

Tegen deze achtergrond is het doel van dit proefschrift om inzicht te verschaffen in het ontstaan en de groei van nationale farmacovigilantie systemen in Afrikaanse landen door verschillende elementen van het nationale farmacovigilantie systeem te bestuderen. De focus van het proefschrift ligt op het bestuderen van de rol en positie van nationale farmacovigilantie centra, de deelname en het bewustzijn van individuen die bijwerkingen rapporteren en beoordelen, en de haalbaarheid van

het genereren van bewijs over de veiligheid en het gebruik van geneesmiddelen in klinische omgevingen met beperkte *resources* in Afrika.

Het proefschrift is georganiseerd in vijf hoofdstukken. **Hoofdstuk 1** is een inleiding en geeft een algemeen overzicht van het onderzoeksonderwerp en de onderzoeksdoelstellingen van het proefschrift zoals hierboven uiteengezet. De daaropvolgende hoofdstukken kunnen als volgt worden samengevat:

In **hoofdstuk 2** bestudeerden we de rol en positie van nationale farmacovigilantie centra in de farmacovigilantie systemen in Afrika. In **hoofdstuk 2.1** hebben we de VigiBase® database gebruikt om een vergelijking te maken tussen de bijwerkingen gerapporteerd vanuit Afrikaanse landen en de bijwerkingen gerapporteerd vanuit de rest van de wereld. Eind september 2015 hadden Afrikaanse landen cumulatief 103,499 bijwerkingen (0.88% van de wereldwijde bijwerkingen) verstuurd naar VigiBase®. De belangrijkste productklassen waarvoor bijwerkingen werden gerapporteerd vanuit Afrikaanse landen verschilden van de productklassen waarvoor bijwerkingen werden gerapporteerd vanuit de rest van de wereld. Deze omvatten nucleoside en nucleotide reverse transcriptase remmers (14.0%), non-nucleoside reverse transcriptase remmers (9.1%), antivirale geneesmiddelen voor de behandeling van hiv infecties (5.5%), de combinatie van een sulfonamide en trimethoprim (3.0%) en angiotensine-converterend enzym remmers (2.4%). De belangrijkste *system organ classes* gerapporteerd vanuit Afrika versus de rest van de wereld omvatten huid- en onderhuidaandoeningen (31.1 % vs. 19.6 %), algemene aandoeningen en aandoeningen op de plaats van toediening (20.9 % vs. 30.5 %) en zenuwstelselaandoeningen (17.5% vs. 19.1%). De leeftijdsgroep van 18 tot 44 jaar domineerde bijwerkingenrapportage vanuit Afrika, terwijl de leeftijdsgroep van 45 tot 64 jaar bijwerkingenrapportage vanuit de rest van de wereld domineerde. We observeerden identieke proporties van vrouwen (57.1% Afrika en de rest van de wereld) en mannen (37.1% Afrika en rest van de wereld) in de database. De resultaten tonen aan dat bijwerkingenrapportage vanuit Afrika substantieel is toegenomen maar dat het totaal aantal gerapporteerde bijwerkingen vanuit Afrika minder dan 1% van het wereldwijde aantal gerapporteerde bijwerkingen in VigiBase® omvat. Voortdurende ontwikkeling en verbeteringen in nationale farmacovigilantie systemen zullen waarschijnlijk bijdragen aan een verdere groei in bijwerkingenrapportage vanuit Afrikaanse landen aan VigiBase®.

Nadat we hadden vastgesteld dat bijwerkingenrapportage in Afrikaanse landen beperkt is, hebben we de organisatorische capaciteit van nationale farmacovigilantie centra bestudeerd als een van de belangrijke organisaties met verantwoordelijkheid voor de rapportagefunctie in het farmacovigilantie systeem. In **hoofdstuk 2.2** verschaften we inzicht in welke activiteiten van nationale centra door strategische leiders als succesvol en onsuccesvol werden gezien en bestudeerden we of het toekennen van succes en mislukking terug te voeren viel op (het gebrek aan)

bepaalde type *resources* en relaties met belanghebbenden. We interviewden 18 strategische leiders van nationale farmacovigilantie centra in Afrika om te achterhalen wat zij succesvolle en onsuccesvolle activiteiten van hun centra achtten. Strategische leiders schreven succesvolle ervaringen het vaakst toe aan het verkrijgen van politieke *resources* (e.g. wettelijk mandaat) en technische *resources* (e.g. *active surveillance database*). Onsuccesvolle ervaringen werden vaak toegeschreven aan een gebrek aan financiële en menselijke *resources*. Belanghebbenden die het vaakst in relatie werden gebracht met succesvolle ervaringen waren de nationale overheid en ontwikkelingsorganisaties, terwijl de nationale overheid en publieke gezondheidsprogramma's het vaakst werden genoemd in onsuccesvolle ervaringen. Op basis van de analyse van interviews concluderen we dat er drie belangrijke uitdagingen zijn voor nationale farmacovigilantie centra in Afrika: (1) een te grote afhankelijkheid van ontwikkelingsorganisaties, (2) schijnbare onverschilligheid van nationale overheden om de centra te ondersteunen nadat ze lid zijn geworden van het PIDM, (3) het betrekken van publieke gezondheidsprogramma's op een duurzame manier.

Om bijwerkingenrapportage aan het nationale farmacovigilantie centrum te bevorderen is het belangrijk dat de verschillende belanghebbenden die betrokken zijn bij farmacovigilantie zich bewust zijn van hun rol in het genereren en gebruiken van data over geneesmiddelenveiligheid. Hoofdstuk 3 evalueerde daarom nationale farmacovigilantie systemen vanuit het perspectief van individuen die bijwerkingen rapporteren (patiënten) en beoordelen (gezondheidszorgprofessionals). In hoofdstuk 3.1 hebben we het bewustzijn van Ghanese patiënten over bijwerkingen en bijwerkingenrapportage bestudeerd. Dit was een studie die bestond uit twee delen: een enquête om het bewustzijn van Ghanese patiënten over bijwerkingen en bijwerkingenrapportage te kwantificeren, en diepte-interviews om in kaart te brengen hoe patiënten bijwerkingen herkennen en de vervolgstappen die ze vervolgens nemen. Deelnemers aan de studie werden geselecteerd in 28 gezondheidszorgfaciliteiten in landelijke en stedelijke gebieden in 4 van de 10 administratieve regio's in Ghana. Van de 491 deelnemers in onze studie had 38% een bijwerking ervaren, waarvan 67% de bijwerking had gerapporteerd aan iemand, en waarvan vervolgens 68% de bijwerking had gerapporteerd aan een arts. Slechts 3% van de 491 deelnemers waren zich bewust van het rapportage systeem van de *Ghana Food and Drugs Authority*. De resultaten laten zien dat er een mismatch is tussen de voorkeuren van patiënten om bijwerkingen te rapporteren aan artsen en de apotheker/ apotheek als eerstelijns contact voor Ghanese patiënten. Gebrekkige kennis over het formele rapportage systeem kan hebben bijgedragen aan de observatie dat patiënten met name persoonlijke redenen noemen om te rapporteren, in plaats van gemeenschappelijke voordelen. We observeerden ook een aantal andere obstakels die bijwerkingenrapportage door patiënten bemoeilijken zoals ondermaatse praktijken

voor het verstrekken van geneesmiddelen en sociaaleconomische verschillen tussen patiënten en gezondheidszorgprofessionals. Deze obstakels verdienen aandacht in vervolgonderzoek.

Er is beperkte kennis over het gebruik van data over geneesmiddelenveiligheid in besluitvorming over geneesmiddelenveiligheid in Afrika. **Hoofdstuk 3.2** is een literatuurstudie om te achterhalen in welke mate farmacovigilantie besluitvorming in publieke gezondheidsprogramma's in Afrika wordt gevoed door lokaal gegenereerd bewijs, en om te bestuderen of het onderliggende bewijs verkregen is via traditionele farmacovigilantie benaderingen of het gebruik van nieuwere methodes en instrumenten. We lieten zien in dit hoofdstuk dat geen enkele belangrijke beleidsbeslissing van publieke gezondheidsprogramma's over geneesmiddelenveiligheid is gebaseerd op data verzameld in Afrika. Data vanuit Afrika lijkt weinig te hebben bijgedragen aan de generatie van veiligheidssignalen over antiretrovirale geneesmiddelen. Hypersensitiviteitsreacties met abacavir zijn bijvoorbeeld beter beschreven in klinische trials in hoge inkomenslanden vergeleken met Afrika waar de hiv/aids ziektelast het hoogst is. Het risico op een myocard infarct door nelfinavir, anemie door zidovudine, huiduitslag door nevirapine en lactische acidose door stavudine zijn allemaal geïdentificeerd in klinische trials en post-registratie onderzoek in niet-Afrikaanse landen. Deze bevindingen zijn verrassend omdat er verwacht kan worden dat de benodigde veiligheidsdata om beslissingen over geneesmiddelenveiligheid te ondersteunen verzameld is in goed gefinancierde publieke gezondheidsprogramma's in Afrika.

Data over het gebruik en de veiligheid van geneesmiddelen afkomstig uit de Afrikaanse klinische praktijk kan nodig zijn om beslissingen te maken over vaak gebruikte producten in Afrikaanse landen. In **hoofdstuk 4** hebben we daarom de haalbaarheid getoetst van het implementeren van een actieve methode voor dataverzameling over het gebruik en de veiligheid van producten in omgevingen met weinig *resources* in Afrika. In **hoofdstuk 4.1** beoordeelden we of de actieve dataverzamelingsmethode *modified cohort event monitoring (mCEM*) kan worden gebruikt om het veiligheidsprofiel van injecteerbaar artesunaat (Inj. AS) in de klinische praktijk te evalueren, in overeenstemming met internationale richtlijnen. In totaal werd Inj. AS toegediend bij 1,103 in aanmerking komende patiënten, waarvan 360 patiënten uit Ghana en 743 uit Oeganda. De incidentie van een bijwerking aan het einde van de *follow-up* onder patiënten behandeld met Inj. AS was 17.9% (197/1103) (95% betrouwbaarheidsinterval: 15.8-20.3). Dit komt overeen met wat gerapporteerd is in klinische studies. De incidentie van veelvoorkomende bijwerkingen onder patiënten behandeld met Inj. AS was relatief laag in de studie. De top vijf gerapporteerde bijwerkingen waren koorts (3.5%), abdominale pijn (2.5%), diarree (1.7%), hoest (1.5%) en asthenie (1.5%). De meeste van deze bijwerkingen traden op binnen 14 dagen na behandeling. De mediane tijd tot aanvang was 9 dagen (interkwartielafstand: 4-14).

Met betrekking tot de gerelateerdheid van deze bijwerkingen aan Inj. AS: 78.9% van koorts (30/38), 63.0% van abdominale pijn (17/27), 68.4% van diarree (13/19), 85.5% van hoest (14/16) en 75.0% van asthenie (12/16) werden beoordeeld als mogelijk gerelateerd. Er waren 17 ernstige bijwerkingen inclusief 13 sterfgevallen. Twee van de sterfgevallen waren mogelijk gerelateerd aan Inj. AS, evenals drie niet-fatale ernstige bijwerkingen: ernstige abdominale pijn, mislukken van de therapie en ernstige anemie. Onze studie is een succesvol voorbeeld van hoe *mCEM* gebruikt kan worden om context specifieke data te verzamelen conform internationale richtlijnen.

Het niet volgen van behandelrichtlijnen kan patiënten blootstellen aan gevaar. De Wereldgezondheidsorganisatie publiceert behandelrichtlijnen voor verschillende behandelingen om veilig en effectief gebruik van deze behandelingen te stimuleren. In **hoofdstuk 4.2** hebben we een *active surveillance* methode gebruikt om te beoordelen of artsen de behandelrichtlijnen van de Wereldgezondheidsorganisatie volgen op het moment dat ze injecteerbare anti-malaria middelen voorschrijven aan patiënten met ernstige malaria. In totaal werden er 1,191 patiënten geïncludeerd in deze studie. Van deze patiënten werd aan 93.0% Inj. AS voorgeschreven, 3.1.% Inj. Arthemeter of Quinine, 32.5% Artimisinin combinatie-therapie (ACT) en 26.1% antibiotica. Van de geïncludeerde patiënten waren er 391 (32.8%) in Ghana en 800 (67.2%) in Oeganda. Er waren 582 (48.9%) vrouwen. De gemiddelde leeftijd was 3.9 jaar (interkwartielafstand: 2-9) en het mediane gewicht was 13 kilogram (interkwartielafstand: 10-20) Van de 1,191 patiënten kregen er 329 (27.6%, 95% betrouwbaarheidsinterval: 25.2%-30.2%) patiënten injecteerbare anti-malaria middelen die werden voorgeschreven volgens de WHO aanbevelingen voor behandeling van ernstige malaria. Inj. AS was het meest voorgeschreven geneesmiddel voor de behandeling van ernstige malaria. Het naleven van de behandelrichtlijn van de Wereldgezondheidsorganisatie bestaand uit op z'n minst 3 doseringen gevolgd door een volledige kuur van ACT was laag. Naleving was hoger voor behandeling van kinderen onder vijf jaar.

De verschillende hoofdstukken in dit proefschrift over het ontstaan en de groei van nationale farmacovigilantie systemen in Afrika bieden een breed perspectief op de uitdagingen waarmee farmacovigilantie systemen in Afrika geconfronteerd worden. De conclusie en discussie in **hoofdstuk 5** laat zien dat de meeste Afrikaanse landen voldoen aan de minimale eisen voor het lidmaatschap van het PIDM. Daarmee beschikken zij over formele farmacovigilantie systemen. Echter, met groeiende farmacovigilantie activiteiten is verdere versterking van de structuren en relaties tussen belanghebbenden wenselijk. De bevindingen in het proefschrift wijzen naar drie terreinen waarop versterking met name nodig is: 1) het bouwen en organiseren van duurzame relaties tussen nationale farmacovigilantie centra, nationale overheden en andere belanghebbenden, 2) het versterken van de rapportage functie van het farmacovigilantie systeem door middel van het creëren van bewustzijn over

bijwerkingen en door de behoeftes en praktijken van patiënten mee te nemen in het ontwerp van rapportagekanalen, 3) het versterken van de afhankelijkheid van en vertrouwen in context specifieke data voor regulatoire besluitvorming. Op basis van de uitgevoerde studies in dit proefschrift raden we ook twee richtingen aan voor toekomstig onderzoek. Ten eerste kan toekomstig onderzoek zich richten op continue evaluatie van het ontwikkelende farmacovigilantie systeem met specifieke aandacht voor de impact van het systeem op geneesmiddelenveiligheid en publieke gezondheid in Afrikaanse landen. Een tweede onderzoeksrichting richt zich op de pogingen in hoofdstuk 4 om *active surveillance* methodes toe te passen in Afrika. Toekomstig onderzoek kan de haalbaarheid van deze methodes verder beoordelen voor andere studie ontwerpen en behandelingen, alsmede aandacht besteden aan het gebruik van nieuwere technologieën en instrumenten voor dataverzameling zoals mobiele telefoons en elektronische patiëntendossiers.

CHAPTER 7

ADDENDUM

CHAPTER 7.1

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7.3

Other Publications

Dodoo ANO, Ampadu HH. Pharmacovigilance in Africa. In: Andrews EB, Moore N, editors. Mann's Pharmacovigilance. New York (NY): John Wiley & Sons; 2014.

CHAPTER 7.4

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Haggar Hilda Ampadu worked in the United States biotech/pharmaceutical/medical device industry for 12 plus years mainly in the areas of clinical trials management and data management. She began her career at Parexel international in Waltham, MA, USA working in diabetes clinical trials for Glaxo Smith Kline (GSK) as a clinical data manager. She then went on to work for various biotech/pharmaceutical companies in the Boston area such as Alkermes, Boston Scientific and Infinity pharmaceuticals and later Depuy Spine (Johnson & Johnson) and Abbot Vascular devices in Santa Clara, California.

Hilda received her bachelor of science in biology degree from the Kwame Nkrumah University of Science and Technology-Kumasi-Ghana and her masters in health care project management from the Boston University, Boston, MA. USA. She is a trained Data Scientist and Certified Clinical Data Manager (CCDM) with the Society of Clinical Data Management; Belgium.

Hilda is the current Acting Director of the African Collaborating Centre for Pharmacovigilance & Surveillance (ACC), Accra, Ghana. She is also a current board member of the International Society of Pharmacovigilance (ISoP) representing Africa. In Ghana, Hilda is a Council/Board member for the Ghana Health Service-Ministry of Health (GHS) and the Accra Technical University-Ministry of Education (ATU).

In November 2014, she started the work presented in this thesis as a PhD Candidate in drug regulatory science at the Utrecht University in the Netherlands. Her research focused on drug regulation policy and pharmacoepidemiology for pharmacovigilance in Africa.