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An Overview of Pharmacovigilance Practice and Management in Sub-Saharan African Countries

Charles Ntungwen Fokunang[1]*, Estella Achick Tembe-Fokunang[1], Ashu Michael Agbor[2], Dobgima John Fonmboh[3], Banin Andrew Nyuki[4], Ralf Duerr[4], Lovet Benyella Fokunang[5], Thomas Lapnet Moustapha[6], Sarah A Tishkoff[7] and Abena Obama Ondoua Marie Therese[8]

[1]Department of Pharmacotoxicology and Pharmacokinetics, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon

[2]Department of Community Oral Health, Université des Montagnes Dental School, Cameroon

[3]Department of Nutrition, Food Science and Bioresource Technology in the College of Technology, The University of Bamenda, Cameroon

[4]Department of Pathology, New York University School of Medicine, New York, NY 10016, USA

[5]Lead Scientist GE Life Sciences CYTIVA, Logan, Utah, USA

[6]Cameroon Specialized Commission for Pharmacovigilance, National Commission for Medicines Registration, Ministry of Public Health, Cameroon

[7]Department of Biology, University of Pennsylvania, Philadelphia, PA 19104; and Center for Global Genomics and Health Equity, University of Pennsylvania, Philadelphia, PA 19104, USA

[8]Department of Pediatrics, Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Cameroon

ABSTRACT

Most sub-Sahara African countries faced with prolonged resource deficiencies suffers specific constraints in establishing a functional and operationally-free pharmacovigilance systems platforms which should guide and in facilitate the generation of vital data to reinforce health information policies and practices. Despite the commendable efforts invested by the different stake holders within such countries to harmonize pharmacovigilance guidelines and regulations, lack of integration and the dependence on pharmacovigilance systems remain major constrains. Other identified difficulties are those associated with the problem of translating data reporting tools into multiple communicable languages, and the inadequacy of the healthcare experts who translates with the patient's population, the pressure imposed by the short consultation time between a patient and a health practitioner. To add to this, there exist issues of community concern like the increasing use of herbal traditional products with anecdotal therapeutic evidence, low quality, self-medication practices, counterfeit and roadside drugs use, substandard medications that are readily accessible to the population. Some prolonged problems are associated with social and political instability, territorial conflicts, little or no access to drug utilization data, which makes it difficult to reliably estimate the true risks of medication use. Pharmacovigilance activities are still at its infancy due to poor and less trained health personnel, lack of budget allocation for health vigilance from the State financial attributions. In addition to the limited investment in pharmacovigilance activities, there is little collaboration between public health programmes and National Medicines Regulatory Authorities (NMRA), especially during mass drug administration for neglected tropical diseases and mass vaccinations. Frequent spontaneous report in SSA is low and this can hinder robust signal detection analyses. This paper attempts to identify the challenges of the practice of pharmacovigilance in sub-Saharan African countries and its implication in health vigilance in the community. In this paper, we review the specific challenges and areas of progress in pharmacovigilance in SSA.

***Corresponding author**

Charles Fokunang, Department of Pharmacotoxicology and Pharmacokinetics, Faculty of Medicine and Biomedical Sciences, University of Yaoundé1, Cameroon.

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Introduction

The World Health Organization (WHO) defines pharmacovigilance (PHV) as the "science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [1-3]. Integrated within this definition are multiple elements relating to the safety of drugs, such as the reporting of substandard and falsified (SF) medicines, medication errors, drug abuse and misuse, exposure to drugs during pregnancy and breastfeeding, therapeutic ineffectiveness, occupational exposure, off-label use, eco-pharmacovigilance (environmental pollution), medical devices and diagnostics, overdose, and

suspected transmission of infectious agents via medicines [4-7]. Sub Saharan African countries (SSA) are faced with specific challenges with effective pharmacovigilance practice. These include the limited integration of pharmacovigilance systems across the regions despite mobilized efforts to harmonize pharmacovigilance rules and regulations in several regional economic communities; the need to translate reporting tools into numerous local languages; high patient-to-healthcare worker (HCW) ratio, with very short consultation times [8]. The scarcity of well-trained pharmacovigilance personnel with little or no budgetary support for these activities from national governments cannot also be underestimated [9]. The issue of the need for high turnover of pharmacovigilance staff whose training involves a substantial amount of resources; little awareness of pharmacovigilance among health care workers (HCWs) are some of the drawback signals [10]. Most decision makers and consumers are concern with many challenges such as; very low reporting rates with poor quality spontaneous reports, which hinders robust signal detection analyses. There are concerns with limited or little collaboration between public health programmes and national medicines regulatory authorities with limited investment in pharmacovigilance activities especially during mass drug administration for neglected tropical diseases. Reports are common on high uptake of herbal and traditional medication, mostly by self-medication especially in regions with social and political conflicts jeopardizing the already fragile systems, some hinterlands having little or no access to drug utilization data, which makes it difficult to reliably estimate the true safety risks of medicine use. [10-14]. It is thus evident that local pharmacovigilance data contributes little to regulatory decisions in most sub-Saharan countries. The WHO Programme for International Drug Monitoring (WHO PIDM) since its inception in 1996, is supporting the advancement of pharmacovigilance activities in resource limited countries.

One of the major challenges in pharmacovigilance is the fact that drug safety evaluation is very rigorous and thorough, and pre-marketing clinical trials however have intrinsic limitations that do not allow to exhaustively evaluate drug safety profile [5]. The studies are conducted on limited numbers of patients that are selected based on regulatory eligibility criteria and not fully representing real-world populations and have limited duration, thus preventing detection of rare and long-term adverse reactions. Therefore, the post-marketing assessment of drugs plays a significant role for a better understanding of drugs' safety profile in to better improve standard of care and fill the gap of information in pre-marketing studies [6].

Scope of Pharmacovigilance

With all the effort of global sensitization and advocacy for pharmacovigilance activities, pharmacovigilance systems in sub-Saharan Africa is mainly focused on adverse drug reaction (ADR)-reporting. However, progress has been made with respect to the additional aspects of PHV reporting within the domain of; Pharmacovigilance in Healthcare Emergency, Database Networks for Post-Marketing Surveillance for Vaccines and Medicines, Artificial Intelligence in Pharmacovigilance, Safety Monitoring of Digital Therapeutics, Pharmacovigilance of Advanced Therapy Medicinal Products, and in the aspects of Eco pharmacovigilance [5,6].

There has been great progress in the pharmacovigilance out of the field of drug safety and regulation where there are still a number of challenges. First of all, COVID-19 pandemic highlighted the importance of pharmacovigilance and proper risk communication during public health emergency. The need to develop advanced methodologies including machine learning techniques and the availability of large amount of electronic healthcare data that offer opportunities for optimizing drug benefit-risk profile evaluation in a global perspective [5]. Finally, innovative therapeutics, such as advanced therapy medicinal products, digital therapeutics, vaccines developed based on advanced technologies, requiring special pharmacovigilance monitoring have been increasingly marketed in recent years, often upon accelerated pathway approval. Some of the challenges and future opportunities in this field has been briefly discussed as follows.

Pharmacovigilance in Healthcare Emergency

During the first waves of the COVID-19 pandemic, the absence of vaccines and drugs for treatment/prevention of COVID-19 led to a rush to repurpose drugs already approved for other indications. As a consequence, a large number of drugs (such as hydroxychloroquine, ivermectin and azithromycin) has been off-label used for the treatment of COVID-19 patients, even if underlying scientific evidence on benefits was of low quality and mostly based on in vitro studies [7,8]. Pharmacovigilance monitoring in this situation has been of relevance in the identification of the risks associated to drugs off-label used, thus reminding the "do not harm first" principle, most especially if no or weak evidence on benefits was available. This is the case of azithromycin, a macrolide antibiotic that has been widely used, for the treatment of COVID-19 patients [9,10]. Its known proarrhythmogenic activity, which can be exacerbated when used in combination with other drugs proposed for COVID-19 treatment (such as hydroxychloroquine), led regulatory agencies to issue warnings against the use of this drug, unless in case of bacterial superinfection occurrence [7].

Accelerated approvals of drugs and vaccines to tackle the COVID-19 pandemic emphasized also the need to expedite and generate safety data in post-marketing setting by identifying and preventing serious risks and ultimately ensuring patients' safety [9].

Database Networks for Post-Marketing Surveillance for Vaccines and Medicines

The increased access to large scale distributed database networks provides new opportunities to monitor the post-marketing safety of vaccines and medicines and to generate real-world evidence to support decision-making. In May 2008 the FDA launched the Sentinel Initiative, an infrastructure analyzing electronic healthcare data to assess the safety of approved medical products [10]. To date, Sentinel has developed one of the largest distributed database networks for the assessment of medical product safety, comprising the Sentinel System, which uses common data models and analytic tools to analyze pre-existing global data, and the FDA-Catalyst, which uses routine queries, interventions and interactions with health plan members and/or providers [10].

Conducting pharmacoepidemiologic studies combining multiple databases is particularly useful when outcomes or exposure of interest are rare, or when evidence is needed from different countries, to generate evidence rapidly and with stronger external validity [6,13]. The combination of several claims databases may provide the statistical power needed to investigate the association between clinically relevant safety outcomes and

specific drug exposure. In this regard, the Italian VALORE project is a good example of how the creation of a distributed network of administrative databases can have a great potential for conducting post-marketing surveillance of biological drugs, including biosimilars, in Italian patients affected by immune-mediated inflammatory diseases [15].

Artificial Intelligence in Pharmacovigilance

The availability of healthcare data has become popular over the last decades and will continue to increase in the near future thanks to massive marketing of digital tools collecting patient-derived data. Big amounts of electronic data give opportunities to apply artificial intelligence (AI) techniques to improve drug safety assessment. Information extraction, using natural language processing (NLP) techniques and text mining to pool relevant information/data from available, largely unstructured sources, has been gaining importance within the field of clinical research. With regards to pharmacovigilance, text mining and NLP methods can be very useful to gather information on adverse drug reactions (ADRs) and drug-drug interactions from various textual sources, supporting researchers and clinicians in monitoring drug safety [12]. Indeed, both public and private entities are currently trying to develop AI tools that can allow to automatically process ADRs [13].

Artificial intelligence and machine learning may also be useful in pharmacovigilance for 1) the automatic execution of tasks associated with case report entry and processing, 2) the identification of clusters of adverse events representing symptoms of syndromes, 3) the conduction of pharmacoepidemiological studies, 4) data linkage, through the conduction of probabilistic matching within datasets and 5) the prediction and prevention of adverse events through specific models using real-world data [14].

Safety Monitoring of Digital Therapeutics

Digital therapeutics (DTx) is one of the most recent advancements of medicine and can be defined as "technologies that deliver medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders"[9]. In orthodox medicines, with the increasing uptake of DTx into clinical practice, a proper post-marketing surveillance of DTx has to be put in place to rapidly identify potential safety signals and establish the safety profile of these technologies. Side effects associated with DTx may be generally less severe and easier to manage than those caused by conventional drugs. However, based on findings from pivotal studies, adverse effects of DTx may still occur to a greater extent than in respective control arms, thus requiring careful post-marketing monitoring [6,9].

Another important aspect of DTx is that they facilitate the collection of massive quantity of post-marketing patient-level data that can be harnessed to re-assess their safety and effectiveness in real-world setting. However, the increase in individual patient-related data poses concerns about data privacy and quality, thus highlighting the need to define a legal framework that allows on the one hand to guarantee individual privacy and on the other hand to transparently share data for research purposes [6].

Pharmacovigilance of Advanced Therapy Medicinal Products

Advanced therapy medicinal products (ATMPs) are drugs for human use that are based on genes, cells or tissue engineering [16]. ATMPs provide new opportunities to restore, correct or modify physiological functions or make a medical diagnosis. Due to their high level of innovations, these drugs usually benefit from accelerated assessment and accelerated approval pathways, thus highlighting the need to generate post-marketing evidence about their benefit-risk profile. However, uncertainties concerning the safety profile of new ATMPs cannot be ascribed only to regulatory pathways. As these medicines often target rare diseases, pre-marketing evidence is generally weak because of inherent limitations of clinical trials due to small number of recruited patients, use of surrogate endpoints and single-arm design [17]. Therefore, post-marketing studies play a key role in generating long term evidence about the safety of these medicines and to fill the knowledge gap of pre-marketing studies.

Ecopharmacovigilance

Ecopharmacovigilance is "the science and activities concerning detection, assessment, understanding and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect both human and the other animal species" , Ecopharmacovigilance is therefore an important issue at the moment and plays a vital role to reduce the environmental risk of pharmaceutical pollutants [18]. As a matter of fact, pharmaceuticals are global environmental pollutants that may be excreted into the environment through different routes, such as the excretion by the patient as parent compound or active metabolites via the sewer system and the release into the waste waters by manufacturers or hospitals and the terrestrial depositions [19]. Several studies have documented the effects of pharmaceutical pollution on various animal species, such as vultures and fish [20]. The role of ecopharmacovigilance is becoming more and more important to control and minimize the sources of pharmaceutical pollution through the detection, assessment and prevention of adverse effects related to the presence of pharmaceuticals in the environment.

Although the detected concentrations of pharmaceuticals in the environment have been shown to be low in low medium income countries (LMIC), (ng/L to µg/L) potential direct and indirect risks for humans exist and should be carefully monitored. It has been reported that sex hormones exert their pharmacological activity at very low concentrations and that exposure to antibiotics may contribute to bacterial resistance [18]. Furthermore, special populations like pregnant women, children and older patients may be more vulnerable to low concentrations of drugs and therefore, addressing issues related to pharmaceutical pollution is one of the main aims of pharmacovigilance following the pandemic exigencies. [15].

Medication Errors and Therapeutic Effectiveness

A recent case study of pharmacovigilance systems in four East African countries showed that medication errors were not well captured in the national pharmacovigilance databases [9]. Reports indicated that health care workers (HCWs) in Uganda for example, were less likely to disclose medication errors due to fear of punitive action from the hierachies [10]. Therapeutic ineffectiveness or lack of therapeutic effectiveness is not well-documented in sub-Saharan Africa. Inference from some countries in these regions showed that consumers are more likely than HCWs to report therapeutic ineffectiveness [11]. Also, as of 2018, Uganda's national pharmacovigilance database showed gaps of data captured on any reports of therapeutic ineffectiveness; for example, in malaria artemisinin-based combination therapies, despite several anecdotal reports

by health care practitioners (HCPs) in that setting [12]. Pharmacovigilance surveillance initiatives on iatrogenic issues that manages medication errors and therapeutic drug monitoring effectiveness are ongoing in many sub Saharan African countries like Nigeria, Ghana, Botswana, Malawi, and the Central African sub regions [4, 9,12].

Pharmacovigilance of Antimicrobial Resistance

Pharmacovigilance databases are of significant value for the indirect surveillance of antimicrobial resistance (AMR) in settings with limited capacity for laboratory-based AMR testing and monitoring. Stimulating the reporting of suspected AMR-related adverse events is a low-cost approach for generating AMR signals for antimicrobial established and sustainable programmes in sub-Saharan Africa [13,14].

Sub-Standard and Falsified Medicines (SF)

A systematic review and meta-analysis of 96 studies on SF medicines in developing economies showed a regional prevalence of 19 % in Africa and 14 % in Asia, the highest estimates of the extent of SF medicines globally, with a market size of up to USD 200 billion. Antimalarials (19 %) and antibiotics (12 %) were the drug categories at highest risk [16]. SF antimalarials contributed to the death of up to 150 000 under-5 children in 39 SSA countries in 2013[17]. Most safety signals picked up by the East African pharmacovigilance systems were related to SF medicines [9,17] which is not surprising given the known high burden in this region [18]. This high burden is linked to weak pharmaceutical governance and poor/nonexistent medicines regulatory systems [19-15]. Africa alone imports 70 % of its drugs, which promotes illicit trade in SF medicines. The inadequate supply chain management and monitoring of medicines in SSA promotes infiltration of these products in the supply chain system and, equally, causes drug stock-outs that encourage consumers to buy medicines from unregulated markets [19,21].

Risk Management and Evaluation of Pharmacovigilance

Pharmacovigilance reports are made using individual case safety reports (ICSRs). The majority of countries in sub-Saharan Africa manually review each ICSR to detect safety signals from the small number of reports in their local databases [21]. Sub-Saharan African countries can also examine other sources of safety signals e.g. peer-reviewed journal publications and can promote quality assurance of their pharmacovigilance data to strengthen signal detection efforts in their local settings [22]. Since 1978, the Uppsala Monitoring Centre (UMC; established in Uppsala, Sweden) on behalf of WHO, have maintained a global repository of ICSRs, VigiBase. A low-cost VigiFlow system, established by UMC, can be used to manage drug safety information at the national level and to share the data globally through VigiBase. SSA countries that are members of the WHO Programme for International Drug Monitoring (WHO-PIDM), can apply VigiLyze to conduct signal detection analyses on national, regional and global safety data in VigiBase, promoting international collaboration [8,23]. High income countries (HIC) use a combination of manual and complex statistical tools with programmed criteria applied to very large complex pharmacovigilance databases that is ahead of human capacity for manual reviews [3,24].

The US Food and Drug Administration (USFDA), and UK Medicines and Healthcare products Regulatory Agency (UK-MHPRA) for example use Quantitative Signal Detection Algorithms (QSDA) in their pharmacovigilance systems [5,25]. However, the current version of VigiLyze provides the same kind of statistical analysis as Quantitative Signal Detection Algorithms, and is accessible to all member countries of the WHO-PIDM [23,26]. It has been reported that methods to enhance signal detection and interpretation, and the prediction of ADRs at both the individual and community levels is evolving, and explore more areas where disparity between HIC and LMIC may continue to widen. Two key examples of pharmacovigilance interventions include individual pharmacogenomic testing and precision medicine as a tool to anticipate and prevent ADRs at individual level, and the use of big data and artificial intelligence to aid signal detection and interpretation [26].

Insight into Pharmacogenomics

Pharmacogenomics is a field that explores relationships between genes and drug effects, with potentials to personalize medical therapy. For clinical scenarios in which a genotype is clearly linked to important outcomes, direct genetic testing has been increasingly used to support clinical decision making, for example testing for the human leucocyte antigens (HLA)-B*1502 allele prior to initiation of carbamazepine to reduce the risk of Stevens–Johnson syndrome [27]. The drug label for carbamazepine recommends HLA-B*1502 screening in all "at-risk populations" and notes heightened risk "across broad areas of Asia", particularly highlighting the strong risk among those of Han Chinese ancestry [27-29]. Such individualized approaches to predict individual risk of ADR represents a paradox of equity as testing is cost-prohibitive and often technologically unavailable in most developing countries, such as in many areas comprising mostly of individuals of highest risk.

Artificial Intelligence

Machine learning is part of artificial intelligence that deals with the ability of machines to learn without having human input. Due to improved computational techniques and the availability of larger datasets in regions where electronic medical records are routine, there is an increasing trend in machine learning adoption in healthcare. Although such innovations have great potential in understanding and predicting safety-related events, these technologies are more difficult to access in sub-Saharan African countries, and mostly rely on electronic medical records, which are still not well developed.

Status of Pharmacovigilance Systems

Most sub-Saharan African countries have little or no regulatory pharmacovigilance systems that can adequately monitor the safety of medicines when compared with the mature pharmacovigilance infrastructure in HIC [28]. To promote best practice in regulatory pharmacovigilance, the WHO in collaboration with Global Fund, established the minimum specifications for a functional pharmacovigilance system updated by WHO in 2020 [14]. The WHO Global Benchmarking Tool have been used to monitor the maturity level of national systems; a maturity scale of 1 is the lowest (regulatory system with minimal activity) and 4 is the highest (regulatory system with advanced performance) [30]. These systems can now be evaluated using the pharmacovigilance performance indicators [31]. Some countries like Cameroon and other Central African states have benefitted from the capacity empowerment of the WHO to formulate policies in the management of PHV within their regions despite lots of administrative and logistic challenges [13].

Harmonization of Pharmacovigilance Systems

Several new guidelines and regulations have emerged across sub Saharan African countries adding complexity to the existing pharmacovigilance requirements leading to duplication of activities. Thus, significant burden has been placed on stakeholders adding little or no benefit for patients or consumers. With some efforts to address harmonization of PHV, the regional economic communities have undertaken special measures to strengthen pharmacovigilance in the regions. So far, from 2009, the African Medicines Regulatory Harmonization (AMRH) initiative has played a foundation role for the establishment of the African Pharmacovigilance network.

The African Medicine Agency (AMA) treaty has been ratified by the countries such as: Algeria, Benin, Botswana, Burkina Faso, Cameroon, Chad, Egypt, Ethiopia, Gabon, Ghana, Guinea, Lesotho, Mali, Mauritius, Namibia, Niger, Rwanda, Seychelles, Sierra Leone, Tunisia, Uganda, Zambia, Zimbabwe and Senegal [32-36]. The AMRH initiative was established to strengthen medicines regulation in Africa by promoting the effectiveness, efficiency, transparency and collaboration of regulatory mechanisms in these settings [36-39]. In 2009, Ghana started the hosting of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, with an objective to promote and strengthen capacity of pharmacovigilance by Ministries of Health and other stakeholders across Africa [40]. This has had major impact on the development of pharmacovigilance in Africa. The training work package and process was provided in English by people with a local perspective, but it excluded Francophone countries in Africa. In 2011, this led to many patient safety-related research and training activities including the pharmacovigilance of medication errors, herbal medicines and vaccines [41].

In Africa, 54 of the 55 countries have National Medicines Regulatory Authorities (NMRAs) or administrative units that perform all or some NMRA functions, although with different strata of growth, expertise and maturity. About 87 % of the NMRAs lack functional pharmacovigilance systems, and none of the African NMRAs have attained the WHO Global Benchmarking Tool maturity level [5,7,39,42]. In SSA, only Ghana and Tanzania have NMRAs attaining the maturity level , which depicts stable and well-functioning systems [3]. In 2016, the African Union (AU) Model Law on Medical Products Regulation, hereafter AU Model Law, was endorsed by the AU Heads of State and Government, to promote medicines regulatory harmonization and collaboration in Africa [43]. The AU Model Law is a legislative framework with one of its five key activities being to harmonize the requirements and processes for ensuring safe medicines in Africa [44]. The AU Model Law was developed and promoted through the AMRH initiative by the New Partnership for Africa's Development (NEPAD), which evolved into the African Union Development Agency NEPAD [45,46]. In 2019, the AU Assembly adopted the AMA treaty, which each Member State was to sign and then enact a corresponding national law to implement this treaty [44]. Rwanda was the first AU Member State to sign the treaty in 2019 and it has subsequently been signed by 16 other Member States [34,47,15,38]. So far, only five Member States have enacted a law to implement the AMA treaty [48-50]. In July 2021, the AMA was established after ratification by the minimum required number of AU Member States [38, 51].

One of the major challenges in sub-Saharan Africa is that there is little or no budgetary support for pharmacovigilance activities by the national governments in most countries; there is heavy dependence on donor funding from North-South collaboration/partnership [30,52]. However, political will is necessary to establish a sustainable budget to recruit full-time pharmacovigilance staff, conduct routine pharmacovigilance trainings and develop national pharmacovigilance policies [53]. Some West African countries have put in place budget allocation for pharmacovigilance activities and the implementation of a more effective and impactful national pharmacovigilance guidelines and regulations [9,39]. Pharmacovigilance activities generate little or no income for NMRAs, and thus limits investment in pharmacovigilance analysis, feedback and expansion [54].

Sources of Pharmacovigilance Data and Methods of Reporting

Data on drug safety can be developed using several methods. In Cameroon for example the Ministry of Health has developed a Pharmacovigilance reporting structure within the Public Health system as illustrated in figure 1. Historically, most sub-Saharan African countries generate PHV data from spontaneous reports. By 2018, SSA and Arab countries had each contributed less than 1 % of pharmacovigilance reports in VigiBase indicating the importance of more proactive approaches including cohort event monitoring (CEM) and targeted spontaneous reporting (TSR) [55].

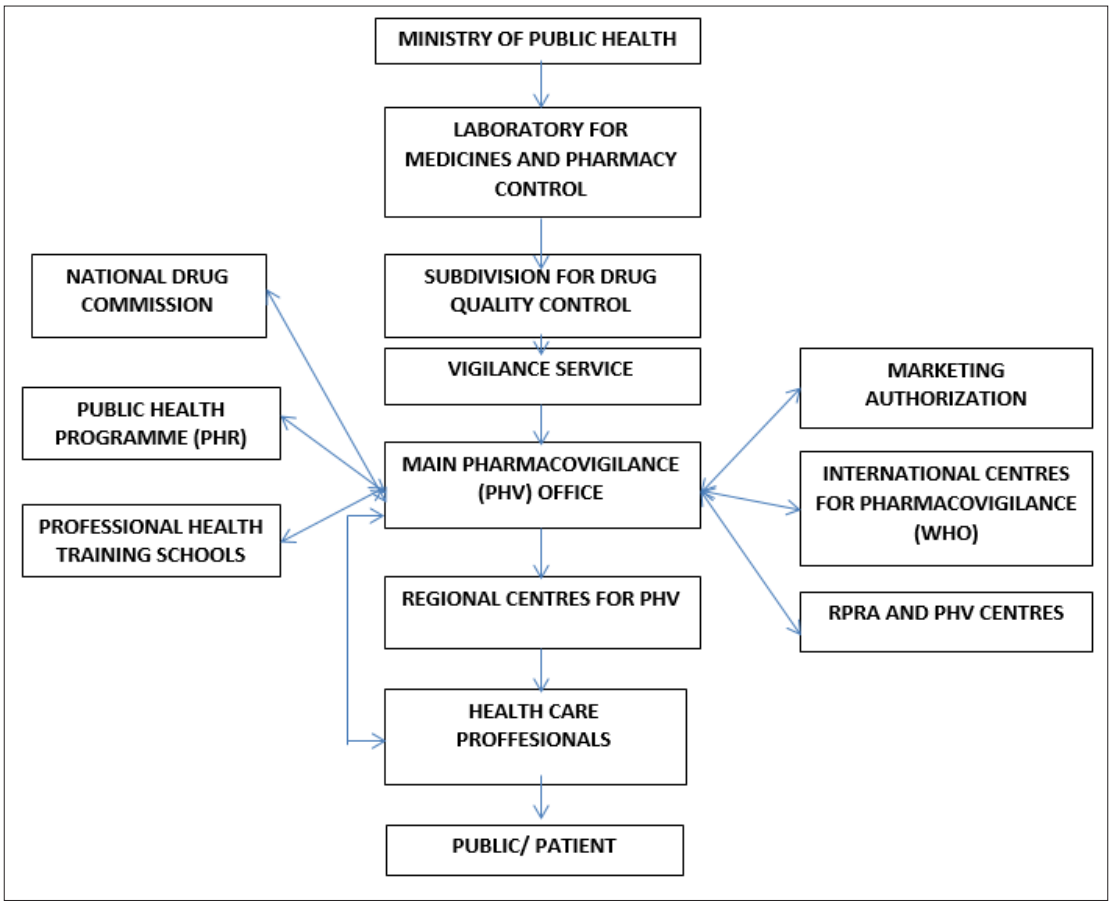

Figure 1: Ministry of Health Pharmacovigilance Reporting Structure within the Public Health system [4].
RPRA= REGIONAL PHARMACEUTICAL REGULATION AUTHORITIES

Sources of PHV Information in SSA

Spontaneous reports, primarily submitted by health care practitioners (HCP) are the main source of pharmacovigilance data for regulatory authorities in SSA. Pharmaceutical companies and market authorization holders (MAHs) submit the largest number of pharmacovigilance reports in the regions, although there are much less represented in SSA [21]. Mapped sites for active surveillance in public health programmes (PHPs) are important sources of data. In SSA, hospital databases are infrequent sources of pharmacovigilance data due to the limited availability of electronic health information systems. Most hospital and health services in the regions are still below standard with health information management (HIMS) [53].

Low Reporting Rates of PHV in Sub Saharan Africa (SSA)

The majority of SSA with national pharmacovigilance systems have weak regulatory policies and minimal pharmacovigilance awareness, resulting in very low reporting rates; and few regulatory decisions on medicines safety are drawn from local data [7,52]. The assessment of four East African countries in 2018 showed that only 1 % of health facilities had reported medicine-related harm in the previous year [9]. Targeted pharmacovigilance awareness campaigns in SSA should at the coordination of public health programmes (e.g. HIV, malaria, tuberculosis [TB]) in order to promote the reporting of medicine-related harm [2]. Other key stakeholders in PHV reporting include Health care workers (HCWs); manufacturers and marketing authorization holders (MAHs); patients/consumers; and higher learning institutions.

Pharmacovigilance Training in SSA

The first training course on cohort events management (CEM) and active surveillance in pharmacovigilance practices (PHPs) on African soil was in Accra, Ghana in 2007, initiated by WHO headquarters, with training support from the Intensive Medicines Monitoring Programme (IMMP) of New Zealand [56-59]. In 2014, Beckmann and colleagues developed a comprehensive model pharmacovigilance curriculum for adoption by educational system platforms and Health Institutions as illustrated in figure 2 and 3 [60].

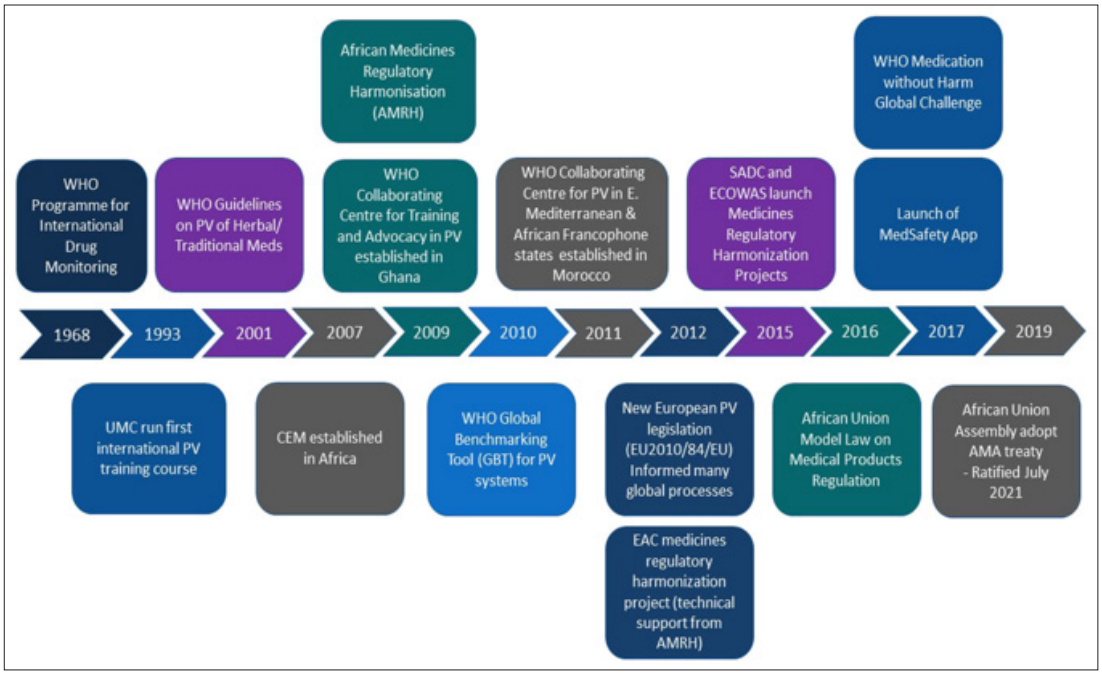

Figure 2: Key Platforms in the Development of Pharmacovigilance Systems in Low- and Middle-Income Countries [14,25].

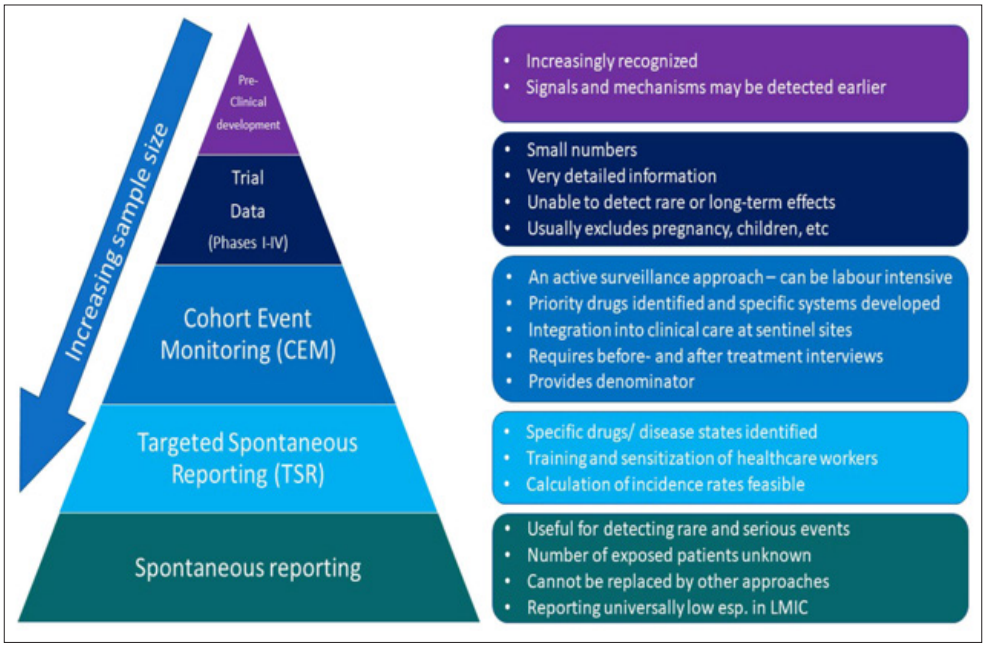

Figure 3: The Pyramid Indicating Spontaneous Reporting, Target Reporting and Cohort Event Monitoring [5].

This model curriculum provides a focused approach for both pre-service and regular in-service training of health care practitioners (HCPs) to improve pharmacovigilance awareness and, ultimately promote reporting. Pre-service pharmacovigilance training is a long-term low-cost intervention that should be integrated in higher education systems [9,59].

Pharmacovigilance education should address three key aspects such as; awareness, knowledge and reporting. HCPs should be aware that medicines can cause adverse drug reactions (ADRs) and should include them in differential diagnosis. They should be knowledgeable about the most frequently used medicines, risk factors for ADRs and other drug-related problems; and understand the purpose of reporting ADRs and other drug-related problems [21,61]. In 2019, the International Society of Pharmacovigilance (ISPhV) organized the first Symposium and Training in Africa, which targeted professionals in the field of pharmacovigilance including regulatory agencies, pharmaceutical companies, academia, healthcare providers and community settings. This event focused on key topics such as: the current pharmacovigilance landscape in Africa; pharmacovigilance during the preapproval phase in Africa; pharmaco-epidemiological methods and other methods that fit with Africa's unique challenges; implementing the concept of Qualified Person in Pharmacovigilance (QPP); pharmacovigilance inspections; and Risk Management Planning

[62]. In 2020, four East African universities in (Ethiopia, Kenya, Rwanda and Tanzania) launched a generic pharmacovigilance core curriculum for undergraduate students of pharmacy, medicine, nursing and dentistry. These countries adopted Lareb's pharmacovigilance curriculum, previously adopted from the WHO model curriculum for universities [63,64]. This focuses on five core pharmacovigilance competencies for future healthcare professionals, namely the ability to understand the importance of pharmacovigilance and drug-induced harm in the context of pharmacotherapy in order to

i. Prevent,
ii. Recognize,
iii. Manage and
iv. Report adverse drug reactions [65].

The curriculum's content could be integrated into exiting courses or can be taught as a standalone programme. Gerritsen and colleagues also demonstrated that the practice-based, skill-oriented pharmacovigilance training method is more effective than the lecture based/knowledge transfer training method in increasing the rate and quality of ADR-reporting by healthcare professionals [66].

The Engagement and Capacity Building of Communities in Pharmacovigilance

Patients or consumers are often excluded from pharmacovigilance activities in SSA, despite awareness of the value of their involvement [67-69]. Since the early 2000s, it has been increasingly recognized that the patient is the primary stakeholder in pharmacovigilance, which has the ultimate aim of ensuring their safe use of medications [70]. This recognition has led to a shift from the patient being a passive recipient to an active participant in their own healthcare. Patient reporting can be defined as, "users of drugs (or their parents or carers) reporting suspected ADRs directly to a spontaneous reporting system" [5,71]. It has been observed that patient reports may differ both qualitatively and quantitatively from healthcare provider-initiated reports, for example in describing effects that have substantial adverse impact on quality of life or that might be sensitive to disclose to a healthcare provider such as sexual dysfunction [72]. A 2017 systematic review of 34 studies confirmed that patient reporting brings novel information particularly relating to severity and impact on daily living, hence complementing the information derived from healthcare providers. Patient reporting will therefore contribute to better decision-making processes in regulatory activities [68,73].

The majority of evidence from patients contribution in PHV has come from Europe, where patient reports have been acceptable since the revised European pharmacovigilance legislation (Directive 2010/84/EU), which has been applicable since 2012 and has introduced a new framework for drug surveillance with proposed valuable changes to improve drug safety [74].This contributions includes the legal right for individual citizens to report suspected ADRs directly to the authorities, and with increasing numbers of countries now making provision for direct patient ADR reporting. Surveying direct patient reporting systems in 50 countries that were part of the WHO programme for international drug monitory (WHO-PIDM) between 2013 and 2014, Margraff and colleagues found out that most countries had implemented a patient ADR reporting system, although many had been very recently established. Many different forms were found to exist worldwide leading to the recommendation that these should be harmonized by considering the strengths and weaknesses of all existing forms [74,75].

On a similar theme, Pal and colleagues reviewed WHO strategy for collecting safety data in public health practitioners (PHPs): patient reports can be incorporated into these structures. Despite increasing recognition of the benefits, and changes to legislature in some poor countries, there are gaps of information from SSA. The International Society of Pharmacovigilance Workgroup on Patient Engagement, assessed patient stakeholder involvement in pharmacoepidemiology research through systematic review. Few publications reported patient or other stakeholder engagement in the design, analysis or reporting of health research. Out of 11 identified studies, 10 were in Europe or North America and a lack of standardized language to report patient involvement was noted [76]. Tanzania is an example of a SSA country that promotes direct patient/consumer reporting of adverse events using a bespoke paper form and are also available in the local language (Swahili) [11]. However, more convenient methods such as digital pharmacovigilance, are needed to promote reporting and to ensure quality. An attempt to review data from 50 countries that participated in the WHO-PIDM, found gaps in data quality such that only 36 countries were represented in the final analysis and all the African countries initially identified in the study were excluded in the data capture [77]. At the end of the study interestingly, stronger and more established pharmacovigilance systems were associated with more patient reporting [78-80].

Several qualitative studies have explored culturally specific community perceptions with regard to patient-initiated ADR-reporting. In some low medium income countries (LMIC) like Thailand, patients were prescribed statins (drugs for lowering cholesterol), and were able to explain how they identified and assessed experiences of suspected ADR and had generally considered the same issues as are present in published causality tools leading the authors to recommend that clinicians encourage patients to self-monitor for potential ADRs and give confidence to their reports [81]. Drawing from a very different perspective, Bukirwa and collaborators, investigated local perceptions and experiences with antimalarial treatment in Uganda and alluded that although community members often recognized adverse events, these were rarely reported either due to it being a known and expected event, or because of concerns relating to the cost of additional visits to healthcare facilities [79]. Community engagement on the benefits of reporting and providing sensitization, training and feedback could be an important driving force to increase patient's participation in PHV data capture [79,80].

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Technological Developments in Digitalization of the Pharmacovigilance Systems

Patient self-reporting may be easier to implement in regions with higher mobile phone penetration. and better platforms for health information system management systems. Cases has been reported where many patients were already aware of ADRs either through personal or family experience, and wanted more information and education on the subject [81]. In China for example, an evaluation of spontaneous ADR reports from children (made by the child or their care giver) were found to comprise only 2.5 % of 3348 reports documented [82]. Whilst access to the internet and ownership of a smartphone are the pre-requisites to using mobile apps, which most individuals in SSA cannot afford, the Unstructured Supplementary Service Data (USSD) and Integrated Voice Response systems are alternative tools that are accessible on both low-tech basic feature mobile

phones and high-tech smartphones and do not use the internet. The USSD and Integrated Voice Response systems are real-time text-driven technologies that allow users to interact directly from their mobile phones by making a selection from a menu.

The USSD interface is a key success factor in the extensive penetration of mobile money banking in rural unbanked SSA, but its use in pharmacovigilance has not yet been evaluated [83]. The Pharmacovigilance Rapid Alert System for Consumer Reporting (PRASCOR) has been used successfully in Nigeria as potential reporters are encouraged to send a text message to a specific number at Nigeria's National Agency for Food and Drug Administration and Control and are then contacted by phone [84]. An example of technological advancement enabling patient self-reporting is seen in the South African MomConnect platform, that allows pregnant women to directly enter information relating to medication exposure and harms [85]. MomConnect was launched in 2014 with the dual intent of providing a platform for health promotion through supportive text messaging to mobile phones of pregnant women (using SMS and USSD technology) and of establishing a registry of pregnancies [85]. Individual interaction through asking questions and reporting symptoms if supported by the system, and hence self-reported pharmacovigilance can be achieved [86]. It has been demonstrated a strong partnership between the South African Ministry of Health and Non-Governmental Organizations with shared launch events, and promotion incorporated into antenatal care has resulted in the system being accessed by almost two thirds of pregnant women across the country. There are some factors unique to South Africa that may have enhanced the success of this initiative such as wide mobile phone coverage, including among females in rural area, and female literacy rates of over 90% [86]. Furthermore, current running costs of approximately $1 million USD annually will be prohibitive to other resource limited countries (RLC) seeking for adoption of the model. More widely, online reporting and mobile phone applications (e.g. Med Safety App and WhatsApp) can be applied to promote pharmacovigilance. The Med Safety App was adapted for resource limited countries from the prototype app developed by the European Union's Innovative Medicines Initiative. Since 2017, Med Safety has been introduced in eight low- and medium-income countries (LMIC) supported by an agreement with WHO, namely Armenia, Botswana, Burkina Faso, Cote d'Ivoire, Ethiopia, Ghana, Uganda and Zambia [87,88].

Communicating Risk Strategies in Pharmacovigilance Systems

A common weakness of pharmacovigilance systems in sub Saharan African countries (SSA) is poor communication and feedback to HCPs and communities. Regular feedback to HCPs and consumers instils in them the importance of reporting medication-related harm, prompting greater involvement in pharmacovigilance activities [53]. Feedback to the public could include warnings on drug safety signals (e.g. drug toxicities, poor-quality medicines) and the regulatory action(s) following the detection of safety signals e.g. product withdrawals. The communication of pharmacovigilance information to HCPs and communities requires mechanisms such as periodic bulletins, newsletters, websites, mobile apps (Med Safety, WhatsApp, Twitter, etc.), SMS, email, toll-free telephone lines, radio and television. In East Africa, Ethiopia and Tanzania have communication plans that are specific for pharmacovigilance. Kenya has a communication plan that is not specific for pharmacovigilance, and Rwanda does not have a communication plan for the implementation of these communication plans, where they exist, has not always been smooth. For instance, in Ethiopia, the bulletins/newsletter should be published four times annually but only one bulletin was published in 2018 [9]. The public can call Kenya's pharmacovigilance centre but the line is not toll-free, which limits the number of would-be callers [9, 12].

Pharmacovigilance in Public Health Practices (PHPS) In SSA

Pharmacovigilance in Public Health Practices PHPs

Public and private healthcare systems in SSA are complemented by dedicated PHPs to address the huge burden of infectious diseases by mass distribution of new and/or repurposed medicines e.g. antiretrovirals, anti-TB medicines, antimalarials, vaccines and medicines for neglected tropical diseases (NTDs) [6]. The safety profile of distributed medicines is rarely well known in these regions, since safety data are primarily generated in HIC whose populations differ socioeconomically, epidemiologically and genetically. Initially, international donors provided substantial funding to PHPs in SSA to increase access to medicines for the priority infectious diseases without proportionate investment in pharmacovigilance infrastructure to monitor the safety of these medicines [6,40,42,89-95]. The direct benefits of providing potentially life-saving medication out ways considerations of risk.

However, it can be argued that integration of pharmacovigilance is ethically essential, as has been illustrated in Figure 4. The harms that can result from neglecting pharmacovigilance can be shown through occurrence of serious adverse events. For example, permanent hearing loss occurs in around half of patients who are given injectable medicines for treatment of multi-drug resistant (MDR) TB such as capreomycin and aminoglycosides [96]. In the recognition of this burden and associated costs, newer potentially less toxic treatment alternatives like bedaquiline are now available.

Figure 4: Ethical imperative for integrating pharmacovigilance activities into public health programmes and mass drug administration [38].

Pharmacovigilance programmes are being introduced into public health programs despite their expense [97]. The number of SSA countries with pharmacovigilance centres linked with PHPs has increased from 10 in 2000 to 35 in 2018 [3,98]. Sentinel sites in PHPs are the commonest source of pharmacovigilance data in SSA with 76 % of pharmacovigilance reports in Kenya are contributed by the HIV programme and 47 % in Ethiopia by the TB programme [51,94]. However, pharmacovigilance structures related to mass drug administration (MDA) campaigns for NTDs remain almost nonexistent.

Pharmacovigilance in Poverty Disease and Neglected Tropical Diseases Programmes

Neglected tropical diseases (NTDs) are a diverse group of viral, bacterial, protozoal and parasitic worm infections or infestations that affect more than 1.5 billion people worldwide [99-101]. The populations most often affected live in poverty less than a (<USD 2/day) with inadequate sanitation [99-102]. The initial WHO target was to eradicate or eliminate these diseases by 2020 through 2 main strategies:

i. P reventive chemotherapy, using mass drug administration (MDA) and
ii. Intensified disease management [2,100,103,104].

In 2017, a billion people received preventive chemotherapy for at least one NTD (Uniting to Combat Neglected Tropical Diseases Africa and Neglected Tropical Diseases; World Health Organization) [105].

Preventive chemotherapy is used in the control of five diseases: soil-transmitted helminthiasis million requiring chemotherapy, schistosomiasis (218 million), lymphatic filariasis (941 million), onchocerciasis (185 million) and trachoma (192 million) [8,34]. Some medicines are effective against several diseases, some against only one. All the medicines are donated by their manufacturers to the NTD programmes. Monitoring the safety of medicines for NTDs is ethically important because these medicines are given regularly, sometimes annually, to all at-risk populations without prior screening or diagnosis [106]. The population exposed to these medicines is often much larger than the infected population. In a benefit–harm perspective, uninfected individuals are exposed to risks of medicine-related harm. [104,107,108]. However, robust pharmacovigilance systems to detect, record and analyze treatment-related adverse events for preventive chemotherapy are scarce [109]. Even where national pharmacovigilance systems exist, no serious attempts are made to document, manage and report adverse events following MDA because the priority of NTD programmes is to maximize MDA coverage by building confidence that the medicines are safe. Treatment-related adverse events are frequently managed and contained at the sites and are not reported to the National Medicines Regulatory Authority (NMRAs) for fear of undermining confidence that may affect the impact of MDA campaigns. For example, in 2017/2018, zero adverse events following MDA were reported to the NMRAs in three East African countries (Kenya, Ethiopia, Tanzania) despite the millions of individuals exposed to MDA during the same period. Furthermore, there is limited or no funding for monitoring the safety of medicines for NTDs in contrast to the priority of PHPs, and there is little or no collaboration between NTD programmes and in-country pharmacovigilance systems. The MDA campaigns are often conducted by community drug distributors or schoolteachers with little or no healthcare background [110-112]. This unacceptable lack of systematic safety follow-up of hundreds of millions of people exposed to preventive chemotherapy for NTDs in LMIC should be reviewed and strengthened. Community dialogue should ensure that needs and concerns of those receiving the drugs are taken into account.

Pharmacovigilance in Noncommunicable Diseases Programmes

Noncommunicable diseases comprise an increasing burden of disease in LMIC, with the major conditions being cardiovascular disease, diabetes mellitus and cancer. Therefore, events relating to medicines safety, including ADRs and drug–drug interactions will increasingly relate to additional classes of medication [113]. Whilst much pharmacovigilance data in LMIC has been drawn from public health programmes focusing on specific conditions, the emergence of increasing co-morbidities and more complex medication regimens underpins the importance of integrated systems [4,114].

Pregnancy Pharmacovigilance

It is increasingly recognized that worldwide, most women require drug treatment at some point during pregnancy [115-117]. Moreover, in LMIC, there are some particular risks. In many settings, the prevalence of HIV in women attending antenatal care far exceeds the national average, and pregnancy increases vulnerability to severe malaria, which in turn can threaten the viability of the pregnancy. Furthermore, no pregnancy screening is done prior to MDA; the probability of exposing women who are not yet known to be pregnant to the drugs is high. It is rare for sufficient pregnancy safety data to be available before a drug is widely introduced into a population that includes women of reproductive potential. Despite increasing recognition that pregnant women should be included in clinical trials to enable assessment of safety and effectiveness even in the field of antiretroviral therapy, there is a median delay of six years between drug licensing and the availability of pharmacokinetic data in pregnancy [118-124]. If clinical trials and pharmacokinetic studies are undertaken, these may not provide the necessary data. The dolutegravir story drew global attention to the challenges and complexities that are faced when introducing a new, effective drug into a population. Dolutegravir is an HIV integrase strand transfer inhibitor that has been shown in nonpregnant populations to reduce the viral load twice as quickly as the existing standard of care therapies, a finding that was later confirmed in trials among Ugandan and South African women presenting with untreated HIV in the third trimester of pregnancy [120,124-127]. In 2016, the Botswanan Ministry of Health decided to transition national policy to dolutegravir based regimens for all people living with HIV. The Tsepamo study had initially been designed to monitor for birth defects with the standard of care efavirenz-based regimens, but adapted to monitor births following dolutegravir exposure in pregnancy. An interim analysis to inform WHO policy revealed the unexpected finding of neural tube defects in 0.9 % (4 out of 426 periconception exposures), which led to a global safety alert and many countries recommended that dolutegravir be withheld in women of childbearing potential[121,128-131]. However, the drug had already been proven effective and better tolerated than the comparator, and communities of women living with HIV raised a well-publicized process calling for clear communication of risks and benefits together with individual choice [46,132]. This highlighted the tension between a public-health policy and the autonomy of individuals, in addition to the fragile birth defect surveillance and pharmacovigilance systems that exist in many LMIC. Furthermore, this emphasized the inability of standard clinical trials or pharmacokinetic studies to generate a sufficient sample size to detect rare events. Mofenson and colleagues argue that to rule out a 2-fold increase in overall birth defect risk, with a 3 % prevalence in the general population, 200 preconception/early first trimester exposures are required; however, for rare defects such as neural tube defects, (0.1 % and ≤0.06 % prevalence in countries without and with food folate fortification, respectively), at least 2000 preconception/ early first trimester exposures are needed to rule out even a 3-fold increase in risk (e.g. from 0.1 to 0.3 %) [118,133-135]. With each subsequent analysis of the dolutegravir data, as the denominator of exposed pregnancies has increased, the signal for association with NTD has decreased, further emphasizing the challenges of obtaining sufficient data for clear clinical recommendations [125,136].

It has long been recognized and emphasized by initiatives including the SGDs and WHO policy, that engagement with antenatal care substantially reduces maternal and infant mortality. Theoretically, pregnancy pharmacovigilance systems could be incorporated into antenatal care, with a complete medical history including all drug exposures prior to and during the current pregnancy being documented, together with follow-up for adverse events during pregnancy and surveillance for birth defects after parturition. However, engagement with antenatal care, particularly in early pregnancy during the time when exposure presents greatest potential teratogenic risk, remains variable and low in many SSA. Furthermore, maternity health records are usually paper-based, contain a level of detail that falls short of what would be required to capture all the necessary information, and are held either by the woman or the healthcare facility and therefore can be difficult to access systematically [137-139].

Paediatric Pharmacovigilance

As with pregnancy, information on the safety and efficacy of a medicine used for neonates (<28 d), infants (28 d–23 mo), children (2–11 y) and adolescents (12–17 y) is limited if individuals from these ages are not included in the premarketing clinical trials, as is frequently the case. Even where children are included in trials, drug toxicity is poorly reported when compared with adults. Particular challenges in understanding medicine-related harms relate to the lack of trial data, that children are often given drugs off label or unlicensed because of lack of specific data and that they have different physiology impacting on pharmacokinetics. Furthermore, some adverse drug events that are subjective in nature may be difficult for a child to describe. In the UK, an analysis of the contribution of children and young people to the UK Medicines and Healthcare products Regulatory Agency yellow card scheme over a 10-year period found that patients from as young as 10 years were able to contribute reports, although most were submitted by adolescents aged 17 or 18 years [21,140]. Most reporting related to vaccines, oral contraceptives, acne medication, anti-infectives and antidepressants. The authors conclusion that children and adolescents are given the knowledge and resources to support themselves in reporting ADRs is consistent with the consensus for engagement and empowerment of adult patients [25,141]. In Uganda, only one in six reports in the national pharmacovigilance database in 2012–2014 were from patients aged <20 years [20, 22].

Most pharmacovigilance reports surrounding pediatric populations have focused on specific populations or disease areas, and generalizability may be limited. Most studies have shown that when systems are established, increasing numbers of ADRs are reported [11,97].

Pharmacovigilance in the Private Health Care Sector in SSA

The national pharmacovigilance infrastructure in most LMIC sits within the public healthcare sector, which presents challenges for the safety monitoring of medicines obtained from the private healthcare sector. Private health facilities in LMIC, particularly in SSA, are scarcely involved in pharmacovigilance activities due to the perception that adverse events are only associated with poor quality healthcare [6]. However, pharmacovigilance is an essential component of high-quality healthcare, and there is a need to promote pharmacovigilance activities in the private sector to foster patient safety [18,142].

Pharmacovigilance in the Pharmaceutical Industry

Stringent pharmacovigilance regulatory requirements are infrequently available or enforced on pharmaceutical companies/ MAHs in developing markets, particularly in SSA [124].

MAHs should, by international standards, employ qualified persons for pharm and submit ICSRs, Periodic Safety Update Reports, Risk Management Plans and Periodic Benefit–Risk Evaluation Reports to their respective NMRAs. Implementing these pharmacovigilance requirements for MAHs is costly for local small-scale manufacturers in SSA and, thus, ought to be adapted to the local situation [6, 143]. Ghana and Kenya were the first in SSA to require MAHs to have QPPVs. In 2018, Tanzania introduced the mandatory requirement for MAHs to have QPPV Furthermore, MAHs in Ethiopia and Tanzania are required to conduct post-marketing surveillance and to submit Periodic Safety Update Reports and Periodic Benefit–Risk Evaluation Reports to their NMRAs [9]. Currently, the involvement of MAHs in national pharmacovigilance systems in SSA is minimal and compliance should be enforced through pharmacovigilance inspections [26,43]. However, NMRAs in SSA should as well build capacity to analyze the reports requested from MAHs [9]. In contrast to the dearth of pharmacovigilance regulation for MAHs in SSA, the majority of ASEAN (7 of 10) have legal frameworks for MAHs to report ADRs to their drug regulatory agencies [19, 21].

Pharmacovigilance for Herbal or Traditional Medications

Herbal and traditional medicinal products (HTM) include manufactured products containing herbal ingredients and simple preparations of herbal substances, the majority of which are derived from plants. Systems include Chinese medicine, Ayurvedic medicine (Indian subcontinent), Aboriginal medicine (Australia), te Rongoa Maori (New Zealand) and many others [16]. Whilst recently increasing in popularity in many well-resourced settings in LMIC, a substantial proportion of the population relies on HTM as their main, or only source of primary healthcare, for reasons including cost, ease of access, perception of safety and sociocultural factors [8,75]. Pharmacovigilance of HTM should be concerned with all aspects of use that have consequences relating to safety and efficacy. Recognizing the importance of this, the WHO published guide lines on safety monitoring and pharmacovigilance for herbal medicines [16]. WHO-PIDM aims to develop a comprehensive global pharmacovigilance strategy that responds to the healthcare needs of LMIC. The UMC launched a traditional medicines programme to stimulate reporting for these products and developed the herbal anatomical therapeutic chemical classification systema and a recommendation for a standardized nomenclature of therapeutic plants [17,67,68]. In 2001, the UMC introduced a traditional medicines surveillance scheme to stimulate reporting and improve the quality of reports of suspected ADRs associated with HTMs. In some settings, the formulation of HTM lends itself to the adoption of regulatory science. The National Medical Products Administration in China proposes to advance the regulatory capacity of traditional Chinese medicines with the adoption of regulatory science. The China Hospital pharmacovigilance system was established in 2015, as a nationwide programme to identify safety signals proactively and to assist the analysis of the association between drug exposure and ADE [79,124]. The Beijing pharmacovigilance database receives adverse drug event data from 94 hospitals in the region, and this has been used to analyse reports arising from the use of traditional Chinese medicine. As an example, between 2004 and 2014, 1393 cases of anaphylaxis were triggered by HTM injections. [127,128]. In Vietnam, 5 % of severe cutaneous ADRs were found to relate to HTM [74,125]. In other settings it can be even more challenging to develop systems to understand the composition, formulation, uses and effects of traditional remedies. To understand effects, mechanism and causality, it is essential to know about precise composition or recipes, their preparation, storage, route of administration and dosing. Furthermore, the dose may be difficult to quantify and variation within the composition may occur seasonally or geographically. Ethnopharmacology is an "interdisciplinary scientific exploration of biologically active agents traditionally employed or observed by man" [75,128]. Drawing from extensive experience in South America, Rodrigues describes how ethnopharmacological surveys describe uses, dosages, sources and methods of preparation of HTM could be adapted to examine safety aspects, proposing a tool comprising a list of questions that could be applied during interview and observational studies, focusing on collecting information and spontaneous reports of ADRs. Establishing a causal relationship can be complex given the combinations of herbs used. It is not yet clear if adopting the proposed tools can yield high quality data enabling such causality assessment [73]. Furthermore, such products are often prescribed outside of conventional healthcare settings. Three quarters of HTM practitioners around Lagos, Nigeria claimed that herbal medicines have no adverse effects, under 7 % had ever documented any ADR, and no documentation was ever forwarded to pharmacovigilance authorities [128].

Whilst spontaneous reporting of HTM ADRs is permissible in most countries, the number of reports received by most countries was very low or insignificant, with reports from traditional prescribers being extremely rare and originating from a single country (Morocco). A need for regulation, training and technical assistance was noted [78, 129]. The significant under-reporting of adverse events from HTM probably relates to lack of awareness of pharmacovigilance issues and reporting systems among those dispensing and using the preparations, administration outside of the mainstream healthcare settings and perceptions of safety. Furthermore, a significant proportion of HTM use is directly initiated by the patient, rather than via a healthcare provider of any type. Once more, it is clear that community engagement and empowerment is important to raise awareness of safety issues, and the need to report these to healthcare providers [15, 112].

Conclusion

The slow progress in Pharmacovigilance initiative in SSA has been a great challenge and request for more effort in strengthening national and Regional pharmacovigilance infrastructures. The harmonization of the regulatory systems across SSA is therefore imperative and significant in order to ensure that budding and/ or nascent pharmacovigilance systems will be inspired by the more established systems. There is thus, a need to consolidate on the most essential aspects of PHV build synergies across countries. Pharmacovigilance systems can be improved by drawing inspiration from the consolidation of the electronic health information systems, setting up large healthcare databases capable of using unique individual identifiers to link medication use data to medicine-related harm data. Large electronic databases can also support the use of statistical techniques and make it possible to evaluate the health impact of pharmacovigilance decisions. At the moment, many countries in SSA in collaboration with WHO have made significant advancement in developing a pharmacovigilance system for drug monitoring of adverse effects and drug interaction within the sub regions which have been proven to be effective though the gap between policy and or administrative decisions is yet to be considerably minimized [144-149].

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