**Pharmacovigilance in Low and Middle-Income Countries: A review with particular focus on Africa**

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**Abstract**

Low- and middle-income countries (LMIC) face unique challenges with regard to the establishment of robust pharmacovigilance systems capable of generating data to inform healthcare policy and practice. These include the limited integration and reliance of pharmacovigilance systems across LMIC despite recent efforts to harmonize pharmacovigilance rules and regulations in several regional economic communities. There are particular challenges relating to the need to translate reporting tools into numerous local languages and the low numbers of healthcare providers relative to number of patients, with very short consultation times. Additional factors frequent in LMIC include high uptake of herbal and traditional medication, mostly by self-medication; disruptive political conflicts jeopardizing fragile systems; and little or no access to drug utilization data which makes it difficult to reliably estimate the true risks of medicines use. Pharmacovigilance activities are hindered by the scarcity of well-trained personnel with little or no budgetary support from national governments; high turnover of pharmacovigilance staff whose training involves a substantial amount of resources and little awareness of pharmacovigilance among healthcare workers, decision makers and consumers. Furthermore, little collaboration between public health programmes and national medicines regulatory authorities coupled with limited investment in pharmacovigilance activities, especially during mass drug administration for neglected tropical diseases and mass vaccinations, produces major challenges in establishing a culture where pharmacovigilance is systematically embedded. Very low spontaneous reporting rates with poor quality reports hinders robust signal detection analyses. This review summarises the specific challenges and areas of progress in pharmacovigilance in LMIC with special focus on the situation in Africa.

**Introduction**

The World Health Organization (WHO) defines pharmacovigilance as the ‘science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems(World Health Organization, 2002). Encompassed within this definition are multiple elements relating to the safety of medication, including the reporting of Substandard and Falsified medicines (SFs), medication errors, drug abuse and misuse, exposure to drugs during pregnancy and breastfeeding, therapeutic ineffectiveness, occupational exposure, off-label use, ecopharmacovigilance (environmental pollution), medical devices and diagnostics, overdose and suspected transmission of infectious agents via medicines(Peters et al., 2021).

Low- and middle-income countries (LMIC) face specific challenges with regard to pharmacovigilance. These include the limited integration of pharmacovigilance systems across LMIC despite recent efforts to harmonize pharmacovigilance rules and regulations in several regional economic communities; the need to translate reporting tools into numerous local languages; large patient-to-healthcare worker (HCW) ratio with very short consultation times; scarcity of well-trained pharmacovigilance personnel with little or no budgetary support for these activities from national governments; high turnover of pharmacovigilance staff whose training involves a substantial amount of resources; little awareness of pharmacovigilance among HCWs, decision makers and consumers; very low reporting rates with poor quality spontaneous reports which hinders robust signal detection analyses; little collaboration between public health programmes and national medicines regulatory authorities; limited investment in pharmacovigilance activities especially during mass drug administration for neglected tropical diseases; high uptake of herbal and traditional medication, mostly by self-medication; regions with disruptive conflict jeopardizing fragile systems; and little or no access to drug utilization data which makes it difficult to reliably estimate the true safety risks of medicine use(Ampadu, Hoekman, Arhinful, Amoama-Dapaah, Leufkens & Dodoo, 2018; Babigumira, Stergachis, Choi, Dodoo, Nwokike & Garrison, 2014; Biswas, 2013; Olsson, Pal & Dodoo, 2015; Olsson, Pal, Stergachis & Couper, 2010). Consequently, local pharmacovigilance data contributes little to regulatory decisions in most LMIC(Olsson, Pal, Stergachis & Couper, 2010).

The WHO Programme for International Drug Monitoring (WHO-PIDM) was established in 1968(WHO-UMC); however, pharmacovigilance activities in LMIC have mostly gathered momentum over the past twenty years. In this paper, we review the specific challenges and areas of progress in pharmacovigilance in LMIC with special focus on the situation in Africa.

**Scope of Pharmacovigilance**

Despite the breadth of pharmacovigilance activities, pharmacovigilance systems in LMIC primarily focus on adverse drug reaction (ADR)-reporting. However, progress is being made with respect to the additional aspects.

*Medication errors*: 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(Barry et al., 2020). Kiguba and colleagues observed that HCWs in Uganda, a country in sub-Saharan Africa (SSA), were less likely to disclose medication errors due to fear of punitive action from the authorities(Kiguba, Waako, Ndagije & Karamagi, 2015).

*Therapeutic ineffectiveness*: Therapeutic ineffectiveness or lack of therapeutic effectiveness is not well-studied in LMIC. In Asia, a recent South Korean study showed that consumers are more likely than HCWs to report therapeutic ineffectiveness(Kim, Jeong, Bae, Baek & Shin, 2019). As of 2018, Uganda’s national pharmacovigilance database had not yet captured any reports of therapeutic ineffectiveness of ACTs despite several anecdotal reports by HCPs in that setting(Kiguba et al., 2020).

*Pharmacovigilance of antimicrobial resistance*: Pharmacovigilance databases are a potentially valuable tool for the indirect surveillance of antimicrobial resistance (AMR) in settings with limited capacity for laboratory-based AMR monitoring. Stimulating the reporting of suspected AMR-related adverse events is a low-cost approach for generating AMR signals for antimicrobial stewardship programs in LMIC(Habarugira & Figueras, 2021a; Habarugira & Figueras, 2021b).

*Substandard and falsified medicines (SFs)*: A systematic review and meta-analysis of 96 studies on SF medicines in LMIC 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(Ozawa et al., 2018). SF antimalarials contributed to the death of up to 150,000 under-five children in 39 SSA countries in 2013(Renschler, Walters, Newton & Laxminarayan, 2015).

Most safety signals picked up by the East African pharmacovigilance systems were related to SFs(Barry et al., 2020), which is not surprising given the known high burden in this region(World Health Organization, 2013). This high burden is attributable to weak pharmaceutical governance and poor/non-existent medicines regulatory systems(Buckley GJ & LO., 2013; Fadlallah, El-Jardali, Annan, Azzam & Akl, 2016; World Health Organization, 2017). Africa imports 70% of its medicines, which promotes illicit trade in SFs. The inadequate supply chain management and monitoring of medicines in LMICs encourages infiltration of these products in the supply chain system and, equally, causes drug stock-outs which encourage consumers to buy medicines from unregulated markets(Buckley GJ & LO., 2013).

**Risk management and evaluation/ Signal detection**

Pharmacovigilance reports are made using individual case safety reports (ICSRs). The majority of LMIC manually review each ICSR to detect safety signals from the small number of reports in their local databases(Chan, Ang & Li, 2017). LMIC can also creatively interrogate 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 own settings(Kiguba, Ndagije, Nambasa & Bird, 2018). Since 1978, the Uppsala Monitoring Centre (UMC; established in Uppsala, Sweden) on behalf of WHO, have been maintaining 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. LMIC which are members of the WHO-PIDM can utilize VigiLyze to conduct signal detection analyses on national, regional and global safety data in VigiBase, promoting international collaboration(WHO-UMC; WHO-UMC, 2020a). High income countries use a mix of manual and complex statistical tools with programmed criteria applied to very large complex pharmacovigilance databases that outpace human capacity for manual reviews(van Manen, Fram & DuMouchel, 2007). For instance, the US Food and Drug Administration (FDA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) use Quantitative Signal Detection Algorithms (QSDA) in their pharmacovigilance systems(Council for International Organizations of Medical Sciences (CIOMS), 2010). However, the current version of VigiLyze provides the same kind of disproportionality statistical analysis as QSDA and is accessible to all member countries of the WHO-PIDM(WHO-UMC, 2020a).

It is noteworthy that methods to enhance signal detection and interpretation, and the prediction of ADRs at both the individual and community levels continue to advance, and bring additional areas where disparity between HIC and LMIC may continue to widen. Two key examples 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(Hussain, 2021).

Pharmacogenomics is a field that explores relationships between genes and drug effects, with potential to “personalize” medical therapy. For clinical scenarios in which a genotype is clearly linked to important outcomes, direct genetic testing is increasingly used to support clinical decision making, for example testing for the HLA-B\*1502 allele prior to initiation of carbamazepine to reduce the risk of Stevens-Johnson syndrome. 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 on those of Han Chinese ancestry(Norvatis, 2009). Such individualised approaches to predict individual risk of ADR represents a paradox of equity as testing is cost-prohibitive and often technologically unavailable in LMIC, including in many areas comprised predominantly of individuals of highest risk.

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. Whilst such innovations have great potential in understanding and predicting safety-related events, these technologies are more difficult to access in LMIC and rely on electronic medical records which again are in their infancy in much of the developing world.

**Status of pharmacovigilance systems in LMICs**

*Overview of regulatory pharmacovigilance in LMIC*: The majority of LMIC have nascent or non-existent regulatory pharmacovigilance systems that cannot adequately monitor the safety of medicines when compared with the mature pharmacovigilance infrastructure in HIC(World Health Organization, 2020). To promote ‘best practice’ in regulatory pharmacovigilance the World Health Organization (WHO) in collaboration with Global Fund established the minimum specifications for a functional pharmacovigilance system in 2010(UNAIDS, 2010). The WHO Global Benchmarking Tool (GBT) can be 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)(World Health Organization, 2018). These systems can also be evaluated using the pharmacovigilance performance indicators(World Health Organization, 2021b).

*Harmonization of pharmacovigilance systems in LMIC:* Several new guidelines and regulations have emerged across LMIC adding complexity to the existing pharmacovigilance requirements including duplication of activities. Thus, significant burden has been placed on stakeholders whilst adding little or no benefit for patients or consumers. In attempt to address this, regional economic communities have undertaken harmonization measures to strengthen pharmacovigilance in LMIC as illustrated in **Figure 1**. These include Association of Southeast Asian Nations (ASEAN); Asia-Pacific Economic Cooperation (APEC); League of Arab States (LAS); African Medicines Agency (AMA); East African Community (EAC); Economic Community of West African States (ECOWAS); South African Development Community (SADC); Pan American Health Organization (PAHO).

Since 2009, the African Medicines Regulatory Harmonization (AMRH) initiative has served as a foundation for the establishment of the AMA(African Union; African Union, 2019b; African Union, 2020; International Federation of Pharmaceutical Manufacturers & Associations, 2018; Ndomondo-Sigonda & Ambali, 2011). 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(Dansie, Odoch & Ardal, 2019; Ncube, Dube & Ward, 2021; Ndomondo-Sigonda & Ambali, 2011; Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017). In 2009, Ghana began to host the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance which aimed to promote the uptake of pharmacovigilance by Ministries of Health and other stakeholders across Africa(Isah, Pal, Olsson, Dodoo & Bencheikh, 2012). This had major impact on the development of pharmacovigilance in Africa. Training was provided in English by people with a local perspective, but it excluded Francophone countries in Africa. In 2011, Morocco became the WHO Collaborating Centre for strengthening pharmacovigilance capacity in the Eastern Mediterranean, Francophone and Arab states. This has enabled numerous patient safety-related research and training activities including the pharmacovigilance of medication errors, herbal medicines and vaccines(Centre Anti poison et de Pharmacovigilance du Moroc [in French]).

In Africa, 54 of the 55 countries have National Medicines Regulatory Authorities (NMRAs) or administrative units that perform all or some NMRA functions - albeit with differing levels of growth, expertise and maturity; 87% of the NMRAs lack functional pharmacovigilance systems(Hye Lynn Choi, Jude Nwokike, Anthony Boni & David Lee, 2012; Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017; World Health Organisation, 2018). None of the African NMRAs are at WHO-GBT maturity level 4. In SSA, only Ghana and Tanzania have NMRAs at maturity level 3, which depicts stable and well-functioning systems(World Health Organisation, 2020; World Health Organization, 2018).

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(African Union Commission, 2016; Glover et al., 2018; Ncube, Dube & Ward, 2021; Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017). The AU Model Law is a legislative framework with one of its five key tenets being to harmonize the requirements and processes for ensuring safe medicines in Africa(African Union Development Agency (AUDA-NEPAD), 2021). 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 (AUDA-NEPAD)(Calder Amanda, 2016; Mwangi JM, 2016).

In 2019, the AU Assembly adopted the AMA treaty(African Union, 2019a; Mukanga D, 2019; Schlesinger D, 2019) which each Member State should sign and then enact a corresponding national law to implement this treaty. Rwanda was the first AU Member State to sign the treaty in 2019(African Union, 2019a; African Union, 2020; International Federation of Pharmaceutical Manufacturers & Associations, 2018), and it has subsequently been signed by 16 other Member States(Ncube, Dube & Ward, 2021). However, only five Member States have enacted a law to implement the AMA treaty(AUDA-NEPAD, 2020). In July 2021, the AMA was established after ratification by the minimum required number of AU Member States(Ncube, Dube & Ward, 2021).

A specific challenge in LMIC is that in most countries there is little or no budgetary support for pharmacovigilance activities by national governments; there exists heavy reliance on donor funding(Ampadu, Hoekman, Arhinful, Amoama-Dapaah, Leufkens & Dodoo, 2018; Biswas, 2013). Yet, political will is necessary to enable establishment of sustainable budgets to recruit full-time pharmacovigilance staff, conduct routine pharmacovigilance trainings and develop national pharmacovigilance policies(Biswas, 2013; Olsson, Pal & Dodoo, 2015; WHO Programme for International Drug Monitoring; Zhang, Wong, He & Wong, 2014). India demonstrated how initial pharmacovigilance initiatives failed until the national government established infrastructure for the national pharmacovigilance system and recruited full-time pharmacovigilance staff(Biswas, 2013). In East Africa, Kenya, Tanzania and Uganda have designated budgets for pharmacovigilance activities which should be enhanced to implement national pharmacovigilance guidelines and regulations more effectively and impactfully(Barry et al., 2020; Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017). Pharmacovigilance activities generate little or no income for NMRAs, which limits investment in pharmacovigilance analysis, feedback and expansion in LMIC(Mehta et al., 2017). Introducing the European Union’s pharmacovigilance fees approach, though attractive, could dampen the growth of pharmacovigilance systems in LMIC(Babigumira, Stergachis, Choi, Dodoo, Nwokike & Garrison, 2014; European Medicines Agency). However change has been proven possible: Lesotho and Namibia are excellent examples of African countries with national governments that fully fund their NMRAs(Ndomondo-Sigonda, Miot, Naidoo, Dodoo & Kaale, 2017).

Key timelines of relevance to the development of pharmacovigilance systems in LMIC are illustrated in **Figure 2**.

**Sources of Data and Methods of Reporting**

Data on drug safety can be harnessed using several methods, as show in Figure 3. Historically, most LMIC data derived from spontaneous reports. By 2018, SSA and Arab countries had each contributed fewer than 1% of pharmacovigilance reports in VigiBase(Ampadu et al., 2016; Bham, 2015; Ekelo, 2017; Vigibase®.) indicating the importance of more proactive approaches including cohort event monitoring (CEM) and targeted spontaneous reporting (TSR).

**Sources of pharmacovigilance information in LMIC**

Spontaneous reports, primarily submitted by HCWs are the main source of pharmacovigilance data for regulatory authorities in LMIC. Pharmaceutical companies and market authorization holders (MAHs) submit the largest number of pharmacovigilance reports in the ASEAN but are much less represented in SSA(Chan, Ang & Li, 2017). Sentinel 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(Mehta et al., 2017). Yet, healthcare databases are common in the ASEAN and are the most important source of pharmacovigilance information in Indonesia(Chan, Ang & Li, 2017; Council for International Organizations of Medical Sciences (CIOMS), 2010).

**Low reporting rates in LMIC**

The majority of LMIC with national pharmacovigilance systems have weak regulatory enforcement and minimal pharmacovigilance awareness, resulting in very low reporting rates; few regulatory decisions on medicines safety are drawn from local data(Olsson, Pal, Stergachis & Couper, 2010). Assessment of four east African countries in 2018 showed that only ~1% of health facilities had reported medicine-related harm in the previous year(Barry et al., 2020). Targeted pharmacovigilance awareness campaigns in LMIC should leverage public health programmes (e.g. HIV, malaria, tuberculosis, etc.) to promote the reporting of medicine-related harm(Peters et al., 2021). Other key stakeholders include HCWs; manufacturers and marketing authorization holders (MAHs); patients/consumers; and higher learning institutions.

**Pharmacovigilance training in LMIC**

The first training course on Cohort Event Monitoring (CEM) and active surveillance in PHPs on African soil was in Accra, Ghana in 2007, initiated by WHO headquarters with training support from the Intensive Medicines Monitoring Programme, New Zealand(Coulter, 1998).

In 2014, Beckmann and colleagues developed a comprehensive model pharmacovigilance curriculum for adoption by education institutions(Beckmann et al., 2014). This model curriculum provides a focused approach for both pre-service and regular in-service training of HCWs to improve pharmacovigilance awareness and, ultimately, promote reporting. Pre-service pharmacovigilance training is a long-term low-cost intervention which should be integrated in higher education systems(Barry et al., 2020). Pharmacovigilance education should address three key aspects: awareness, knowledge and reporting. HCWs should: be *aware* that medicines can cause ADRs and should include them in differential diagnosis; 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(Herrera Comoglio, 2020).

In 2019, the International Society of Pharmacovigilance (ISoP) organized the first-of-a-kind 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 delivered on key topics including; the current pharmacovigilance landscape in Africa, pharmacovigilance during the pre-approval phase in Africa, pharmaco-epidemiological methods and other methods that fit with Africa’s unique challenges, implementing the concept of Qualified Person in Pharmacovigilance, pharmacovigilance inspections and Risk Management Planning(International Society of Pharmacovigilance, 2019).

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(PROFORMA, 2020a; PROFORMA, 2020b). This focuses on five core pharmacovigilance competencies for future healthcare professionals, namely i) the ability to understand the importance of pharmacovigilance and drug-induced harm in the context of pharmacotherapy in order to ii) prevent, iii) recognize, iv) manage and v) report adverse drug reactions(van Eekeren et al., 2018). The curriculum’s content could be integrated into exiting courses or taught as a standalone programme. Gerritsen and colleagues have 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(Gerritsen, Faddegon, Dijkers, van Grootheest & van Puijenbroek, 2011).

**Engagement and empowerment of communities in pharmacovigilance**

Patients or consumers are often excluded from pharmacovigilance activities in LMIC, despite awareness of the value of their involvement(Defer et al., 2021; Inacio, Cavaco & Airaksinen, 2017; Kiguba, Karamagi, Waako, Ndagije & Bird, 2014). Since the early 2000s, it has been increasingly recognised that the patient is the primary stakeholder in pharmacovigilance, which has the ultimate aim of ensuring their safe use of medications(Härmark & van Grootheest, 2008). 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(van Grootheest, de Graaf & de Jong-van den Berg, 2003). It has been noted that patient reports may differ both qualitatively and quantitatively from healthcare provider-initiated reports, for example describing effects which have substantial adverse impact on quality of life or which might be sensitive to disclose to a healthcare provider such as sexual dysfunction(Blenkinsopp, Wilkie, Wang & Routledge, 2007; van Grootheest, de Graaf & de Jong-van den Berg, 2003). 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. Thus, patient reporting will contribute to better decision-making processes in regulatory activities(Inacio, Cavaco & Airaksinen, 2017).

The majority of evidence has come from Europe, where patient reports have been acceptable since the revised European pharmacovigilance legislation (Directive 2010/84/EU) which came into force in 2012 and introduced a new framework for drug surveillance and proposed valuable changes to improve drug safety(European Union, 2010). This includes the legal right for individual citizens to report suspected ADRs directly to the authorities(Borg, Aislaitner, Pirozynski & Mifsud, 2011).

Increasing numbers of countries make provision for direct patient ADR reporting. Surveying direct patient reporting systems in fifty countries that were part of the WHO-PIDM between 2013 and 2014, Margraff and colleagues found 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(Margraff & Bertram, 2014). On a similar theme, Pal and colleagues reviewed WHO strategy for collecting safety data in PHPs: patient reports can be incorporated into these structures(Pal, Duncombe, Falzon & Olsson, 2013). Despite increasing recognition of the benefits, and changes to legislature in some HIC, evidence from LMIC remains scanty. The ISoP Workgroup on Patient Engagement assessed patient stakeholder involvement in pharmacoepidemiology research through systematic review. Few publications mention patient or other stakeholder engagement in the design, analysis or reporting of research: of 11 identified studies, ten were in Europe or North America. A lack of standardised language to report patient involvement was noted(Camelo Castillo et al., 2019). Tanzania is an example of a SSA country which promotes direct patient/consumer reporting of adverse events using a bespoke paper form and made available in the local language (Swahili)(Barry et al., 2020). However, more convenient methods, e.g. digital pharmacovigilance, are needed to promote reporting and ensure quality. An attempt to review data from 50 countries that participate in the WHO-PIDM, found gaps in data quality so that only 36 were represented in the final analysis; all six African countries initially identified were then excluded. Unsurprisingly, stronger and more established pharmacovigilance systems were associated with more patient reporting(Inácio, Gomes, Airaksinen & Cavaco, 2018).

Several qualitative studies have explored culturally specific community perceptions with regard to patient-initiated ADR-reporting. Thai patients prescribed statins 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 (Chaipichit, Krska, Pratipanawatr, Uchaipichat & Jarernsiripornkul, 2014), leading the authors to recommend that clinicians encourage patients to self-monitor for potential ADRs and give credence to their reports. Drawing from a very different perspective, Bukirwa 2008 investigated local perceptions and experiences with antimalarial treatment in Uganda. Although community members often recognised 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. Community engagement on the benefits of reporting and providing sensitisation, training and feedback will be important aspects to increase participation(Bukirwa et al., 2008; Ndagije et al., 2019).

**Technological Advances and Digital Pharmacovigilance Systems**

Patient self-reporting may be easier to implement in regions with higher mobile phone penetration. In Saudi Arabia, Kassem 2021 found that many patients were already aware of ADRs either through personal or family experience, and wanted more information and education on these(Kassem, Alhabib, Alzunaydi & Farooqui, 2021). In China, an evaluation of spontaneous ADR reports from children (made by the child or their carer) were found to comprise only 2.5% of 3348 reports(Li et al., 2014).

Whilst access to the internet and ownership of a smartphone are the pre-requisites to using mobile apps, which most individuals in LMIC, particularly in SSA, cannot afford, the Unstructured Supplementary Service Data (USSD) and Integrated Voice Response (IVR) 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 IVR systems are real-time text-driven technologies which 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(Ayo C. K., Ukpere W. I., Oni A., Omote U. & D., 2012) but its use in pharmacovigilance has not yet been evaluated. The Pharmacovigilance Rapid Alert System for Consumer Reporting (PRASCOR) has been used successfully in Nigeria. 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(Ogar et al., 2018).

An example of technological advance enabling patient self-reporting is seen in the South African MomConnect platform which allows pregnant women to directly enter information relating to medication exposure and harms(Barron et al., 2018). 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(Barron et al., 2018). Individual interaction, through asking questions and reporting symptoms is supported by the system, and hence self-reported pharmacovigilance can be achieved(Heekes et al., 2018). Strong partnership between the South African Ministry of Health and Non-Governmental Organisations with shared launch events, and promotion to be 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 which 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 greater than 90%(Heekes et al., 2018). Furthermore, current running costs of approximately $1 million USD running costs annually will be prohibitive to other LMIC seeking to adapt the model.

More widely, online reporting and mobile phone applications (e.g. Med Safety App and WhatsApp) can be leveraged to promote pharmacovigilance. The Med Safety App was adapted for LMIC from the prototype app developed by the European Union’s Innovative Medicines Initiative. Since 2017, Med Safety has been introduced in eight LMICs supported by an agreement with WHO, namely Armenia, Botswana, Burkina Faso, Cote d’Ivoire, Ethiopia, Ghana, Uganda and Zambia(WEB-RADR). India developed and implemented its own mobile app(Prakash et al., 2019).

**Risk communication between Pharmacovigilance Systems and HCWs and Communities**

A common weakness of pharmacovigilance systems in LMIC is poor communication and feedback to HCWs and communities. Regular feedback to HCWs and consumers instills in them the importance of reporting medication-related harm, prompting greater involvement in pharmacovigilance activities(Mehta et al., 2017). 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 HCWs and communities entails mechanisms such as periodic bulletins, newsletters, websites, mobile apps (e.g. Med Safety, WhatsApp, Twitter, etc.), SMS, email, toll-free telephone lines, radio and television. In East Africa, Ethiopia and Tanzania have communication plans which are specific for pharmacovigilance; Kenya has a communication plan which is not specific for pharmacovigilance; and Rwanda does not have a communication plan(Barry et al., 2020). The implementation of these communication plans, where they exist, has not always been smooth. For instance, in Ethiopia, the bullen/newsletter should be published four times annually but only one bulletin was published in 2018(Barry et al., 2020). The public can call Kenya’s pharmacovigilance centre but the line is not toll-free, which limits the number of would-be callers(Barry et al., 2020).

**Pharmacovigilance in Public Health Programmes in LMIC**

*Overview of pharmacovigilance in public health programmes:* Public and private healthcare systems in LMIC are complemented by dedicated Public Health Programmes (PHPs) to address the huge burden of infectious diseases through mass distribution of new and/or repurposed medicines e.g. antiretrovirals, antituberculosis medicines, antimalarials, vaccines and medicines for neglected tropical diseases (NTDs)(Olsson, Pal & Dodoo, 2015). The safety profile of distributed medicines is rarely well known in LMIC since safety data are primarily generated in HIC whose populations differ socioeconomically, epidemiologically and genetically. Initially, international donors provided substantial funding to PHPs in LMIC to increase access to medicines for the priority infectious diseases without proportionate investment in pharmacovigilance infrastructure to monitor the safety of these medicines(Bill & Melinda Gates Foundation; Gavi; Hye Lynn Choi, Jude Nwokike, Anthony Boni & David Lee, 2012; Isah, Pal, Olsson, Dodoo & Bencheikh, 2012; Olsson, Pal & Dodoo, 2015; PEPFAR; The Global Fund; UNICEF; UNITAID); the immediate benefits of providing potentially life-saving medication eclipsed considerations of risk. However, it can be argued that integration of pharmacovigilance is ethically essential as illustrated in **Figure 4**. The harms that can result from neglecting pharmacovigilance can be illustrated 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 tuberculosis (MDR-TB) e.g. capreomycin and aminoglycosides(Seddon, Godfrey-Faussett, Jacobs, Ebrahim, Hesseling & Schaaf, 2012); in recognition of this burden and associated costs, newer, potentially less toxic treatment alternatives e.g bedaquiline and delamanid are being introduced despite their expense(Reuter & Furin, 2018). The number of SSA countries with pharmacovigilance centres linked with PHPs has increased from 10 in 2000 to 35 in 2018(Ampadu, Hoekman, Arhinful, Amoama-Dapaah, Leufkens & Dodoo, 2018; World Health Organisation, 2017c). Sentinel sites in PHPs are the commonest source of pharmacovigilance data in SSA: 76% of pharmacovigilance reports in Kenya are contributed by the HIV programme and 47% in Ethiopia by the tuberculosis programme(Barry et al., 2020). However, pharmacovigilance structures related to Mass Drug Administration (MDA) campaigns for NTDs remain almost non-existent.

*Pharmacovigilance in Neglected Tropical Diseases programmes:* Neglected Tropical Diseases (NTDs) are a diverse group of viral, bacterial, protozoal and parasitic worm infections or infestations which affect more than 1.5 billion people worldwide(Caplan & Zink, 2014; Drugs for Neglected Diseases Initiative (DNDi), 2010; Uniting to Combat Neglected Tropical Diseases Africa and Neglected Tropical Diseases). The populations most often affected live in poverty (<USD 2/day) with inadequate sanitation(Caplan & Zink, 2014; Drugs for Neglected Diseases Initiative (DNDi), 2010; World Health Organization). The initial WHO target was to eradicate or eliminate these diseases by 2020(World Health Organisation, 2012a; World Health Organisation, 2017b) through two main strategies: i) preventive chemotherapy using MDA and ii) intensified disease management(Caplan & Zink, 2014; Drugs for Neglected Diseases Initiative (DNDi), 2010).

In 2017, one billion people received preventive chemotherapy for at least one NTD(Uniting to Combat Neglected Tropical Diseases Africa and Neglected Tropical Diseases; World Health Organization). Preventive chemotherapy is used in the control of five diseases: soil-transmitted helminthiasis (834 million requiring chemotherapy), schistosomiasis (218 million), lymphatic filariasis (941 million), onchocerciasis (185 million) and trachoma (192 million). 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 imperative because these medicines are given regularly, sometimes annually, to all at-risk populations without prior screening or diagnosis(World Health Organisation, 2006; World Health Organisation, 2011b). Thus, 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(World Health Organisation, 2011a; World Health Organisation, 2017b). Yet, robust pharmacovigilance systems to detect, record and analyse treatment-related adverse events for preventive chemotherapy are scarce (World Health Organization, 2006). 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 NMRAs for fear of undermining confidence which may negate the impact of MDA campaigns. By 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 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(Barry et al., 2021). 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 of antituberculosis, antiretroviral and antimalarial medicines:* Pharmacovigilance relating to other PHPs has gained more attention. In 2013, WHO published guidelines for PHPs which fortified spontaneous reporting systems with more robust pharmacovigilance methods such as Cohort Event Monitoring (CEM) and Targeted Spontaneous Reporting (TSR)(World health Organisation, 2007; World Health Organisation, 2009; World health Organisation, 2012b; World Health Organization, 2006). CEM and TSR can generate verifiable denominator data to measure the risks of medicines(Pal, Duncombe, Falzon & Olsson, 2013). Ghana and Nigeria have successfully implemented CEM to evaluate the safety of artemisinin-based combination therapies for malaria treatment and Uganda has applied TSR to monitor the safety of tenofovir, an antiretroviral drug(Bassi et al., 2013; Dodoo et al., 2014; Ndagije et al., 2015). Collaboration between PHPs and NMRAs is critical to strengthening pharmacovigilance systems but is often limited (Ampadu, Hoekman, Arhinful, Amoama-Dapaah, Leufkens & Dodoo, 2018; Ndagije et al., 2015). Some LMIC have demonstrated coordinated action between their national expanded programmes on immunization and NMRAs(Salman, Topf, Chandler & Conklin, 2021), which is in line with the recent merging of the directorates of vaccines and medicines safety surveillance at WHO((PvPI), 2017). The WHO is implementing the smart safety surveillance (3-S) project to strengthen, expand and streamline pharmacovigilance in LMIC. This project will optimize the post-marketing surveillance of new priority medicines and vaccines that have not been tested elsewhere. LMIC will share expertise and experiences, and build in-country capacity for pharmacovigilance (Iessa et al., 2021; World Health Organisation, 2017c).

*Antituberculosis medicines:* New and repurposed antituberculosis medicines have recently been introduced to manage MDR-TB. WHO introduced the active drug safety monitoring and management (aDSM) framework to strengthen the pharmacovigilance of these in LMIC(World Health Organisation, 2015a), see **Figure 5**. The aDSM programme primarily focuses on the identification, management and reporting of serious adverse events linked to new regimens for MDR-TB and extensively drug-resistant TB (XDR)(World Health Organisation, 2015a).

The novel MDR-TB medicines, bedaquiline, delamanid and pretomanid received accelerated approval by the United States Food and Drug Administration (USFDA), European Medicines Agency (EMA) and the Japanese and Korean regulatory authorites(Conradie et al., 2020; Diacon et al., 2014; Skripconoka et al., 2013) based on limited clinical data from HIC and were scaled up rapidly in LMIC despite the gaps in knowledge about safety(Conradie et al., 2020; Diacon et al., 2014; Skripconoka et al., 2013; World Health Organisation, 2017c). Clofazimine and linezolid have been repurposed for MDR-TB treatment, are prescribed with little experience and for longer than their recommended duration of use, which increases the risk of drug-related toxicities, and have not yet been approved for this indication(Falzon et al., 2011). The aDSM framework should improve pharmacovigilance relating to these agents. In Asia, India has created an elaborate pharmacovigilance system which automatically transmits bedaquiline-related safety data between the TB programme and the national pharmacovigilance database(World Health Organisation, 2017a). However, the creation of a global aDSM database for new and repurposed medicines alongside WHO’s VigiBase duplicates rather than consolidates pharmacovigilance activities in LMIC where resources are in limited supply. The recent introduction of the PAVIA project, supported by EDCTP, in Ethiopia, Tanzania, Eswatini and Nigeria is an attempt to improve the pharmacovigilance of MDR-TB and supports the integration of aDSM with general pharmacovigilance(PhArmacoVIgilance Africa (PAVIA), 2020).

*Antiretroviral medicines:* The rapid scale up of the new HIV drug dolutegravir as the main agent in both first-line and second-line antiretroviral therapy, together with concurrent tuberculosis preventive therapy (especially isoniazid) uptake prompted adoption of the aDSM model for monitoring the safety of these medicines e.g. in Uganda(Ministry of Health Uganda, 2020). Through such processes, Uganda described previously unrecognized signals relating to glucose dysregulation(Lamorde et al., 2020) and are currently investigating potential memory disturbances(National Drug Authority, 2021). Considerations relating to dolutegravir and pregnancy are described below.

*Antimalarial medicines*: Cohort event monitoring has been successfully implemented in the active safety monitoring of artemisinin-based combination therapies in several SSA countries including Burkina Faso, Ghana, Kenya, Mozambique, Nigeria, Tanzania and Zimbabwe(Baiden et al., 2015; Suku et al., 2015).

**Pharmacovigilance in non-communicable diseases programmes**

Non-communicable diseases (NCDs) 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(Kuemmerle et al., 2021). 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.

**Pregnancy Pharmacovigilance**

It is increasingly recognised that worldwide, most women require drug treatment at some point during pregnancy(Lupattelli et al., 2014). 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 which includes women of reproductive potential. Despite increasing recognition that pregnant women should be included in clinical trials to enable assessment of safety and effectiveness(Eke et al., 2021; Fairlie et al., 2019; Weld, Bailey & Waitt, 2021), even in the field of antiretroviral therapy, there is a median delay of 6 years between drug licensing and the availability of pharmacokinetic data in pregnancy(Colbers, Mirochnick, Schalkwijk, Penazzato, Townsend & Burger, 2019). If clinical trials and pharmacokinetic studies are undertaken, these may not provide the necessary data required.

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 which had been shown in non-pregnant populations to reduce the viral load twice as quickly as the existing standard of care therapies(Walmsley et al., 2013), a finding that was later confirmed in trials among Ugandan and South African women presenting with untreated HIV in the third trimester of pregnancy(Kintu et al., 2020; Waitt et al., 2019). 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)(Zash et al., 2019; Zash, Makhema & Shapiro, 2018) which led to a global safety alert and many countries recommending that dolutegravir be withheld in women of ‘childbearing potential’. However, the drug had already been proven effective and better tolerated than the comparator, and communities of women living with HIV raised a well-publicised process calling for clear communication of risks and benefits together with individual choice(2019). 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 emphasised the inability of standard clinical trials or pharmacokinetic studies to generate a sufficient sample size to detect rare events. Mofenson and colleagues(Mofenson et al., 2019) argue that to rule out a twofold 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(Zaganjor et al., 2016), at least 2000 preconception/early first trimester exposures are needed to rule out even a threefold increase in risk (e.g. from 0.1% to 0.3%). 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 emphasising the challenges of obtaining sufficient data for clear clinical recommendations(Polly Clayden, 2019).

It has long been recognised and emphasised 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 LMIC. Furthermore, maternity health records are usually paper-based, contain a level of detail which 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.

The supplementary table summarises key studies describing the incorporation of pregnancy pharmacovigilance and birth outcome surveillance into the routine monitoring systems.

In summary, prospective, comprehensive data of drug exposure during pregnancy and correlation with birth outcome data are required. In LMIC, the best solutions will be those which dovetail with existing systems and infrastructure to enable a sustainable intervention which has buy-in from all the relevant stakeholders. Training of HCWs on the importance of accurate collection of such data should be prioritised.

**Paediatric pharmacovigilance**

As with pregnancy, information on the safety and efficacy of a medicine used for neonates (<28 days), infants (28 days – 23 months), children (2-11 years) and adolescents (12-17) is limited if individuals from these ages are not included in the premarketing clinical trials, which 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 which 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 MHRA yellow card scheme over a 10-year period found that patients from as young as 10 years of age were able to contribute reports, although most were submitted by adolescents aged 17 or 18 years. 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(Bhoombla et al., 2020). In Uganda, only one in six reports in the national pharmacovigilance database in 2012-2014 were from patients aged less than 20 years(Kiguba, Ndagije, Nambasa & Bird, 2018).

Most pharmacovigilance reports surrounding paediatric populations have focussed on specific populations or disease areas, and generalisability may be limited. Most studies have shown that when systems are established, increasing numbers of ADRs are reported(Morales-Ríos et al., 2020; Priyadharsini, Surendiran, Adithan, Sreenivasan & Sahoo, 2011).

**Pharmacovigilance of vaccines**

It is imperative that vaccine administration is accompanied by robust pharmacovigilance given that these products are used widely in populations who are currently well; the risk-benefit considerations are such that even low rates of adverse events may be unacceptable.

*Vaccines in children:* The WHO minimum requirements of a country’s capacity to monitor vaccine safety are; i) a national causality assessment committee for adverse events following immunization (AEFI) and, ii) reporting a minimum of 10 AEFIs per 100,000 surviving infants annually(World Health Organization). In the past decade, LMIC reported AEFIs less frequently to VigiBase and with a lower proportion of serious AEFIs than HIC(Salman, Topf, Chandler & Conklin, 2021) possibly because of the establishment of vertical EPI programmes that do not communicate well with the NMRAs. Collected AEFIs are not incorporated into VigiBase, partly also because EPI programmes have not adopted the ICH E2B standard for recording and exchange of ICSR data. The NMRAs in Africa have limited capacity to monitor vaccine safety(World Health Organization). However, the WHO Africa region registered the largest increase in the proportion of countries that are able to report >10 AEFIs during the past decade; from 15% (n=7) of 47 countries in 2010 to 57% (n=27) in 2019(Salman, Topf, Chandler & Conklin, 2021). The observed growth in AEFI reporting in Africa is attributable to WHO’s increased investment in the region; that is, conducting vaccine safety trainings and supporting the establishment of national AEFI surveillance systems including standardization of the AEFI data collection tool(World Health Organization, 2012).

LMIC could further improve their vaccine safety surveillance systems by strengthening collaboration between National Expanded Programmes on Immunization (EPI) and NMRAs. Such collaboration could improve the rate and quality of AEFI reporting to foster timely detection and response to vaccine safety signals(World Health Organization, 2012). For instance, the total number of AEFIs in Eritrea, an African country, increased 90-fold during three years (11 in 2016; 966 in 2018) when their NMRA and EPI formed an integrated AEFI surveillance system. Eritrea enhanced its vaccine safety surveillance system by training HCPs and establishing an AEFI causality assessment committee(Salman, Topf, Chandler & Conklin, 2021).

*COVID-19 vaccines:* By March 2021, more than forty COVID19vaccine candidates were in phase III clinical trials or had received emergency approval(2021a). By April 2021, almost 1 billion doses of vaccines had been administered globally albeit inequitably with 40 doses per 100 people in North America and 1.1 doses per 100 people in Africa(Acharya, Ghimire & Subramanya, 2021; Holder., 2021; Naniche et al., 2021). The WHO Global Vaccine Safety Initiative promotes harmonization of the reporting of AEFIs and adverse events of special interest (AESI)(2021b). A recent survey in more than 100 LMIC showed that the existence of well-functioning child immunization programs is not a strong predictor of country readiness to deliver and monitor the safety of COVID-19 vaccines(World Bank, 2021). The greatest challenge of COVID-19 vaccine safety monitoring will be faced by pharmacovigilance systems in LMIC, particularly in Africa, where weak or non-existent regulatory pharmacovigilance systems prevail. African countries over-rely on paper-based forms for AEFI reporting but should embrace electronic tools of AEFI reporting e.g. Med Safety, DHIS2 and WHO’s VigiFlow(African Union Development Agency – NEPAD: AU-3S, 2021). LMIC should draw from the experience of scaling up the pharmacovigilance of antiretrovirals, antituberculosis medicines and antimalarials e.g. a different set of important AEFIs and AESIs could arise in LMICs with different clinical patterns of local diseases from HICs e.g. HIV, malaria, TB, nutrition status.

COVID-19 vaccines target very large healthy adult populations seeking to reduce their risk of developing severe disease(Naniche et al., 2021). Thus, LMIC should promote transparency and effective monitoring of vaccines to foster public trust in COVID-19 vaccination programs. Global collaboration is imperative for LMIC to tap into the well-developed pharmacovigilance systems in HIC which promote such transparency and rapid feedback to the public. LMIC could be guided to give priority to the signal evaluation of serious/unexpected adverse events to avoid overwhelming their pharmacovigilance systems and wastage of scarce resources. Benign adverse events e.g. headache, injection site pain, fever etc. could be evaluated when additional resources are available(African Union Development Agency – NEPAD: AU-3S, 2021). A WHO-approved list of AESIs for COVID-19 in LMIC has been published(Brighton Collaboration, 2021). The African Vaccine Regulatory Forum is a good platform to promote international collaboration and the African Advisory Committee on Vaccine Safety will support African countries on pharmacovigilance and COVID-19 vaccine safety(African Advisory Committee on Vaccine Safety (AACVS); World Health Organisation, 2015b). The PAHO Member States developed a pharmacovigilance dashboard to support the introduction and safety monitoring of COVID-19 vaccines on the American continent(PAHO, 2021).

**Pharmacovigilance in the private healthcare sector in LMICs**

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 LMICs, particularly in SSA, are scarcely involved in pharmacovigilance activities due to the perception that adverse events are only associated with poor quality healthcare(Olsson, Pal & Dodoo, 2015). 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.

**Pharmacovigilance in the pharmaceutical industry in LMICs**

Stringent pharmacovigilance regulatory requirements are infrequently available or enforced on pharmaceutical companies / marketing authorization holders (MAHs) in developing markets, particularly in SSA(World Health Organisation, 2017a). MAHs should, by international standards, employ qualified persons for pharmacovigilance (QPPVs) and submit Individual Case Safety Reports (ICSRs), Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs) and Periodic Benefit-Risk Evaluation Reports (PBRERs) to their respective NMRAs. Implementing these pharmacovigilance requirements for MAHs is costly for local small-scale manufacturers in LMICs and, thus, ought to be adapted to the local situation(Olsson, Pal & Dodoo, 2015). Ghana and Kenya were the first LMICs in SSA to require MAHs to have QPPVs. In 2018, Tanzania introduced the mandatory requirement for MAHs to have QPPV(Barry et al., 2020). Furthermore, MAHs in Ethiopia and Tanzania are required to conduct post-marketing surveillance and to submit PSURs and PBRERs to their NMRAs. Currently, the involvement of MAHs in national pharmacovigilance systems in SSA is minimal and compliance should be enforced through pharmacovigilance inspections(International Society of Pharmacovigilance, 2021). However, NMRAs in SSA should as well build the capacity to analyze the reports requested from MAHs(Barry et al., 2020). In contrast to the dearth of pharmacovigilance regulation for MAHs in SSA, the majority of ASEAN (seven of 10) have legal frameworks for MAHs to report ADRs to their drug regulatory agencies(Chan, Ang & Li, 2017).

**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(Barnes, 2020). Whilst recently increasing in popularity in many well-resourced settings(Barnes, Mills, Abbot, Willoughby & Ernst, 1998), 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. Pharmacovigilance of HTM should be concerned with all aspects of use that have consequences relating to safety and efficacy.

Recognising the importance of this, the WHO published guidelines on safety monitoring and pharmacovigilance for herbal medicines(World Health Organisation, 2004). 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 (ATC) classification systema and a recommendation for a standardized nomenclature of therapeutic plants(Farah et al., 2006; WHO-UMC, 2020b). 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 program to identify safety signals proactively and to assist the analysis of the association between drug exposure and ADE(Liang et al., 2021). 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(Li et al., 2018). In Vietnam, 5% of severe cutaneous ADRs were found to relate to HTM (Nguyen et al., 2019).

In other settings it can be even more challenging to develop systems to understand the composition, formulation, uses and effects of traditional remedies. In order 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’(Mukherjee, Venkatesh & Ponnusankar, 2010). Drawing from extensive experience in South America, Rodrigues describes how ethnopharmacological surveys to 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, focussing 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(Rodrigues & Barnes, 2013). 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(Awodele, Daniel, Popoola & Salami, 2013). Looking more broadly, Skalli and colleagues surveyed HTM pharmacovigilance in African members of the WHO-PIDM in 2014. 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(Skalli & Bencheikh, 2015).

The significant under-reporting of adverse events from HTM likely 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.

**Recommendations**

In LMIC, a stepwise approach to strengthening national pharmacovigilance infrastructure based on available resources is recommended, moving from a core framework to advanced capacity. The harmonization of regulatory systems across LMIC ensures that weak or non-existent pharmacovigilance systems draw from the more established systems. Thus, LMIC in Africa ought to focus on the most essential functions and to build reliance between countries(Iessa et al., 2021; World Health Organization, 2021a).

Pharmacovigilance systems in LMIC should invest in electronic health information systems to support the establishment of large healthcare databases capable of using unique individual identifiers to link medication use data with medicine-related harm data. Large electronic databases enable the use of statistical techniques and make it possible to evaluate the health impact of pharmacovigilance decisions(Fadlallah, El-Jardali, Annan, Azzam & Akl, 2016; Mehta et al., 2017). These databases should be built using international standards for record keeping, allowing easy exchange of data between pharmacovigilance partners. The databases provide denominator data to estimate the risks of medicines using pharmacoepidemiologic methods. The potential sources of robust pharmacovigilance data for pharmacoepidemiologic studies are cohort studies (including CEM),record-linkage studies, registries (e.g. insurance registries, pregnancy and birth outcomes registries) and randomized controlled trials(Calmy et al., 2020; Mehta et al., 2017; Venter et al., 2019).

LMIC should strengthen the pharmacovigilance of frequently used medicines used to treat NTDs and non-infectious diseases (diabetes, high blood pressure, stroke, etc.) due to the rising morbidity, mortality and healthcare costs associated with these diseases(Tipping, Kalula & Badri, 2006).

LMIC, particularly in Africa, should accelerate global and regional regulatory harmonization to foster collaboration and reliance. Competent regulatory authorities in Africa engender trust and could provide the main ingredient of any useful roadmap towards building the desired collaboration. Thus, reliance on the work and regulatory decisions made by other African countries in their region with more competent regulatory authorities facilitates faster approval of novel and essential medicines – making the medicines more accessible to their populations(World Health Organization, 2021a). In-country harmonization of national regulatory and programmatic pharmacovigilance activities should also be a priority.

Over the past two decades, considerable progress has been made, and focus on the priority areas summarized in Table 1 will improve pharmacovigilance in LMIC, and so ultimately, improve the health of the populations.

**Funding statement**

CW is supported by a Wellcome Clinical Research Career Development Fellowship 222075/Z/20/Z. CW is an investigator on the DolPHIN-2 Study, funded by Unitaid. RK is supported by a Makerere University Research and Innovations Fund grant (no grant number).

**Authorship statement**

All authors contributed equally to the manuscript

**Conflict of interest disclosure**

No author has any conflict of interest.

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**Table 1: Pharmacovigilance Priorities in LMIC**

|  |
| --- |
| Creating a culture where pharmacovigilance is prioritised |
| Training on pharmacovigilance to be embedded into Medicine, Pharmacy, Nursing and Midwifery curricula |
| Feedback provided to healthcare workers, policy makers and consumers in response to pharmacovigilance reports |
| Regular in-service training opportunities and easy-to-access updates on pharmacovigilance |
|  |
| Engagement and empowerment of communities to report medicine-related harms |
| Harmonisation of patient reporting tools |
| Media and public engagement activities to raise awareness of pharmacovigilance |
| Consultation with and involvement of community representatives, particularly for Mass Drug Administration |
| USSD approaches to enable patient self-reporting using standard mobile phone |
|  |
| Systems and infrastructural development |
| Stepwise approach to strengthening national pharmacovigilance infrastructure based on available resources, moving from a core framework to advanced capacity |
| Harmonization of regulatory systems across LMIC to ensure that weak or non-existent pharmacovigilance systems draw from the more established systems |
| Engaging pharmaceutical companies and MAH as partners in national pharmacovigilance systems through regulations compatible with international standards |
|  |
| Learning both within and between countries |
| Building on local strengths and clinical priorities |
| Targeted pharmacovigilance awareness campaigns in LMIC should leverage public health programmes (e.g. HIV, malaria, tuberculosis, etc.) |
| Priority medication should be identified (i.e. for CEM, TSR approaches) |
|  |
| Databases and reporting systems |
| Increasing move to electronic medical records and reporting systems |
| Databases built using international standards for record keeping, allowing easy exchange of data between pharmacovigilance partners |

Figure Legends

Figure 1 Global economic regions of relevance to pharmacovigilance in LMIC

Figure 2 Key Milestones in the Development of pharmacovigilance Systems in LMIC

Figure 3 Hierarchy of sources of individual case safety reports

Figure 4 Ethical imperative for integrating pharmacovigilance activities into PHP and MDA

Figure 5 Relationship between National TB control programmes and Pharmacovigilance Systems

Diagram

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Figure 1

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Figure 2

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Figure 3

Diagram, website

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Figure 4

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Figure 5