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Pharmacovigilance in resource-limited countries

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In the past 20 years, many low- and middle-income countries have created national pharmacovigilance (PV) systems and joined the WHO's global PV network. However, very few of them have fully functional systems. Scientific evidence on the local burden of medicine-related harm and their preventability is missing. Legislation and regulatory framework as well as financial support to build sustainable PV systems are needed. Public health programs need to integrate PV to monitor new vaccines and medicines introduced through these programs. Signal analysis should focus on high-burden preventable adverse drug problems. Increased involvement of healthcare professionals from public and private sectors, pharmaceutical companies, academic institutions and the public at large is necessary to assure a safe environment for drug therapy. WHO has a major role in supporting and coordinating these developments.

KEYWORDS: adverse drug reactions • consumer involvement • drug regulation • harm • low and middle income countries • medicines • patient safety • Pharmacovigilance • public health programs

Medicine-related harm

The full scope of pharmacovigilance

When pharmacovigilance (PV) first developed as a consequence of the thalidomide tragedy in the 1960s, the focus was on studying adverse drug reactions (ADRs) to medicines after they have been authorized for use [1]. The most commonly used classification of these adverse effects are augmented (Type A) or bizarre (Type B) reactions, primarily distinguishing between pharmacological effects and hypersensitivity reactions [2]. Research on medicine-related hospitalizations carried out over the past 35 years has demonstrated that approximately 50% of medicine-related patient harms leading to hospitalization are preventable, that is, are associated not with the intrinsic properties of the medical product itself, but with the way it has been prescribed, dispensed, administered or used [3,4]. Thus, current PV methods take a much broader overview of PV focusing thereby on safety surveillance through the entire lifecycle of a medicinal product. In the 1990s, counterfeit medicines emerged as a major threat to public health and confidence

in healthcare systems, particularly in resource-limited countries [5]. WHO defines PV as the 'science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems' [6]. Thus, the WHO definition alludes to all harms associated with a medicine including harms due to poor quality manifesting, for example, as absence of expected effect. In other words, there is scope within PV operations to trace and detect the presence of substandard and poor quality medicines, particularly when these products would lead to adverse events in patients.

Prioritizing access to medicines

In the early years, PV in low- and middle-income countries (LMIC) was 'prominently' absent, probably because improving access to life saving medicines was more of a priority; investing in PV systems to monitor the safety of products that were not available to the majority of the population was considered a luxury. The WHO essential medicines- and pre-qualification programs, and investments by Global Health Initiatives like the Global Fund

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(GF), UNITAID, Global Alliance for Vaccines and Immunization (GAVI), Bill & Melinda Gates Foundation (BMGF) and others have improved access to medicines and vaccines in LMICs. One consequence of these developments is that many more individuals now have access to treatment and are consequently at risk of treatment-related adverse effects, especially in communities with limited education and few trained healthcare professionals (HCPs) to guide the safe and appropriate use. The need for PV in all countries including LMIC is therefore obvious and WHO and its partners are working hard to support member countries to establish effective national PV systems. PV is now getting attention and most LMICs are beginning to establish PV systems.

Healthcare systems: the context

Healthcare systems in resource-limited countries are generally more complex and fragmented than in the developed world. Most countries have primary, secondary and tertiary care available in the public sector but also various kinds of privately organized healthcare facilities, either for-profit or not for profit. Various donors, faith-based organizations and non-governmental organizations such as the Red Cross and Médecins Sans Frontières are represented in the latter sector. As most resource-limited countries are also facing huge public health challenges, primarily from communicable diseases but lately also from non-communicable diseases, they have established dedicated public health programs (PHPs) to efficiently meet these challenges. Examples of such PHPs are national immunization programs and programs against malaria, HIV/AIDS, tuberculosis and neglected tropical diseases. Such PHPs are often supported by WHO and Global Health Initiatives like the GF, UNITAID, United Nations International Children's Emergency Fund, GAVI, President's Emergency Plan for AIDS Relief, BMGF and so on [7–12]. Many of these PHPs use and distribute large quantities of vaccines and medicines, often without a close collaboration with the pharmaceutical supply system in the public and private sector. In addition, a large part of the population in these countries use or are dependent on traditional medicines either by choice or because of limited access to essential medicines in remote areas.

Because of the fragmented healthcare systems and weak regulatory oversight, the pharmaceutical supply chain in resource-limited countries is characterized by poor enforcement of legislation; under these conditions, substandard/spurious/falsely labeled/falsified/counterfeit (SSFFC) medicines and vaccines can easily penetrate the supply chain. Sub-standard and counterfeit medicines pose a huge threat to human health and monitoring these threats to patients has also become a part of PV.

Establishing PV systems

What we have learnt

Every country is unique and there is no general recipe on how to establish a PV system in a country. However, by observing and comparing the process of development of PV in many resource-limited countries over time, it is possible to identify certain common features. Typically:

- Based on the author's experience in supporting PV centers for more than three decades, PV is often initiated by a few dedicated HCPs who, on observing treatment-related harm in patients, take it upon themselves to introduce a reporting and learning system in their environment with a view to minimizing the *recurrence of such harms in the future*. Such individuals may be based in clinical or academic settings and can often convince decision makers to organize a systematic collection of observations of suspected medicine-related harm.
- PV activities invariably start with spontaneous reporting of individual case safety reports (ICSRs) because this is the least resource-demanding method that may be initiated without major investments.
- In the early implementation phase, countries would often apply for formal training in PV methodology, such as those offered by the WHO's Program for International Drug Monitoring through its network of collaborating centers, by professional associations such as the International Society of Pharmacovigilance or by a limited number of academic institutions. Another alternative way of learning the basics of PV is through internships in well-established PV centers.
- Some countries only start PV as part of a regional or sub-regional initiative involving economic communities, such as the Economic Community of West African States or the East African Community [13]. In these settings, one or two countries take the lead in establishing PV centers and are often used by the others for attachments and capacity building.

Challenges to PV in LMIC

Initiating a stable reporting process for ICSRs in resource-limited settings involves many challenges.

- HCPs are often few and have many patients to attend to during a day, with little time to fill a form and report a suspected ADR.
- HCPs may be unwilling or uncomfortable reporting ADRs with treatments due to fear of perceptions of professional error or culpability, lack of clear legal provisions to guarantee confidentiality of submitted reports, lack of trust in the integrity of authorities and so on.
- Distributing and returning completed reporting forms can be complicated or expensive. Postal services and electronic networks in LMICs often fail. Mobile telephone networks are often the most widespread and reliable. If reporting is organized to follow strict and cumbersome reporting lines, for example, from local level to district to region and finally to a national level, delays at any of these intermediate steps will result in long delays in receipt of the report and in overall information sharing.
- Reporting forms need to be available in all local languages and PV experts need to be familiar with all those languages. This can be a huge challenge in countries with several local languages.
- Self-medication often accounts for a large proportion of medicines use. Due to the costs involved as well as the dearth of trained HCPs, especially in rural and remote areas, consumers often seek help from traditional healers or unregistered

peddlers rather than from formal health facilities. Consequently asking registered HCPs about their observations and experiences of adverse effects of medicines can at best capture only a limited proportion of medicine-related harm in the population. Direct patient reporting may therefore have to be considered to ensure that all medicine-related harms are captured in these settings.

Individual commitment and enthusiasm alone will not be sufficient to manage the challenges facing PV in LMIC; it would be necessary to engage the influence, authority and resources of public institutions to build a full-fledged, sustainable national PV system that meets the specifications of the WHO's 'Minimum Requirements for a Functional Pharmacovigilance System' [14].

Legal framework & political commitment

Establishing a national PV system requires a strong legal framework and political commitment. Only few LMIC countries, for example, Nigeria, Eritrea and the Philippines [15–17] have established a national PV policy, although several others have provisions in their national medicines legislation mandating regulatory authorities to establish PV systems [18]. It is essential that all countries have clear and published national policies for PV.

Influencing through evidence

The best way of convincing political leaders on the need for PV in their country is by presenting evidence of the burden of medicine-related harm in the population. Unfortunately, very few studies have been carried out in resource-limited settings to document the humanitarian and economic burden of medicine-related injuries. Available studies indicate that the extent of harm caused by medicines in LMICs is comparable with that in high-income countries [19–21]. As the number of publications relating to medicine-related harm in LMICs is low, there is a great need for additional research to be carried out on the burden of harm, including those due to medication errors. Cooperation between LMICs for example, by sharing similar study designs and protocols may provide robust and comparable data for decision making.

Sustaining PV systems

Although countries may have regulatory provisions to set up PV systems, it is only when those provisions are matched with a regular and sustainable budget that real action and long-term planning can be achieved. Good examples exist in countries like India and PR China. In India, initiatives have been taken by various academic and research institutions as well as the regulatory authority to establish PV in the country since the mid-1980s. Only when a budgeted staff position for PV was created by the Government in 2010 was the PV system effectively established in the whole country [22]. In PR China, the Federal Government invested heavily in PV training in the provinces, leading to a rapid increase in reporting of ICSRs to the National Coordinating Center [23].

Human resources

Training opportunities

Professionals with knowledge of PV are rather few in all countries because training on this cross-cutting specialty is offered only in very few places. Until very recently, such training was not offered in any LMIC. The Uppsala Monitoring Centre (UMC), the oldest WHO Collaborating Center for International Drug Monitoring, has been offering its flagship course in PV since 1993. However, only a limited number of health professionals from LMIC have had the financial resources to attend this course in the past. The early development of national PV programs very much depends on the few trained individuals and their ability to enthuse and train others. The establishment of the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra (2009) and the WHO Collaborating Centre for Pharmacovigilance in Rabat (2011) has improved the opportunities for PV education and training in LMIC, especially in Africa. The Spanish regulatory agency has contributed to capacity building in Latin America by organizing a series of PV training courses in several countries over many years.

Remuneration

A particular problem in resource-limited countries is the comparatively low salary offered in the public sector. Specialist competence is often highly sought after and better paid in the private sector or by foreign non-governmental organizations operating in the same country. These factors sometimes lead to a high turnover of PV professionals, which severely hampers the development, continuity, and expansion of the national PV program.

Need for broader competencies

A notable trend is the engagement of pharmacists in PV. This tendency is positive but not if these pharmacists are replacing physicians. PV centers in LMICs often have no or very few physicians on the staff, possibly for cost reasons. A clinician is trained and experienced in differential diagnosis, which plays a key role in discerning an ADR from an underlying disease. Because of an inadequate mix of competencies many PV centers are not well prepared for providing advice on managing the adverse events observed in a clinical setting.

PV in universities

There is a great need for introduction of PV in undergraduate and graduate levels in teaching institutions for all health professionals all over the world. WHO has established a WHO collaborating center in the Netherlands with the specific task of integrating PV within the curricula for health training institutions [24]. Recently, India made it compulsory for all medical colleges to include PV training in the undergraduate curriculum. This is an interesting development and one worth considering by other countries.

Regulatory PV

In high-income countries, PV has become very much dominated by regulatory aspects, particularly after the initiation of

the ICH process in 1990. In this regulatory environment, the major onus for PV is on the marketing authorization holders (MAH; see Good Vigilance Practice, introduced in the EU [25–27]). MAHs are mandated to submit to regulatory authorities, for example:

- Expedited ICSRs.
- Periodic safety update reports/periodic benefit risk evaluation reports.
- Risk management plans.
- Results of post-authorization safety studies.

MAHs are also required to have a qualified person for PV available at all times to respond to any safety concerns from authorities and to effectively manage the PV system.

PV & MAHs

Although many resource-limited countries are striving toward more stringent regulatory systems, very few have so far introduced and implemented the full set of PV requirements for MAHs as set out by the ICH guidelines. Instituting such requirements would favor multinational companies but may disadvantage local manufacturers and generic medicines producers who would find it hard and/or expensive to establish PV systems, including quality assurance, a PV master file and internal audits as required by good vigilance practice guidelines. Local generic manufacturers in LMICs would lose some of their competitive advantage of low manufacturing costs. PV, as required in ICH countries, can thus become a major disincentive for local and generic manufacturers who nonetheless must accept that they have responsibility for the stewardship of their products through the lifecycle of these products. A more pragmatic approach is therefore needed to ensure that countries are able to implement the essential elements of PV that are consistent with ICH standards, but adapt some of the other stipulations to suit the local environment.

PV in regulations

Even in resource-limited countries with relatively well-functioning PV systems, the regulatory basis for the system is sometimes weak or non-existent, which makes it difficult for the authority to enforce regulatory actions based on safety concerns. However, many of these countries have developed PV guidelines [28] and also training material for PV promotion and advocacy.

Low-cost reporting solutions of international standards

In a global perspective, it is of course very important for national PV systems to set up and maintain ICSR databases that are compatible with the international standard format for ICSR-reports, the ICH-E2b. The international standard allows easy exchange of ICSRs between countries and between regulatory authorities and MAHs. This is key for the early identification and analysis of new safety signals. Establishing E2b-compatible systems is expensive but LMICs can utilize the VigiFlow data management system offered and maintained at a very low cost by the UMC [29] as it integrates E2b standards within it. LMICs that

use VigiFlow can also accept ICSRs in this standard format from their local MAHs, further facilitating smooth and timely exchange of drug safety information among all stakeholders.

PV systems & models that work

Because of a lack of political stability and good governance in some LMICs it may be favorable to locate the coordination of a PV system away from Ministry of Health or equivalent and run the PV center, for example, in a university or hospital environment where effects of political fluctuations are often less dramatic. Observations of the authors based on country visits to several LMICs as well as discussions with key opinion leaders indicate that promising PV setups have been brought to a halt or failed to develop further because of changes in the political environment. It might be economical to combine PV activities with, for example, a drug information and poison information service. The PV center in Morocco is a good example of such a model [30,31]. However, it is important to note that running a national PV center outside the national drug regulatory agency or authority presents several challenges, including the need to communicate PV findings for national decision making on medicines registration and use.

Capturing lack of effect through PV

Because poor quality or counterfeit products pose a threat to public health, in many resource-limited countries, it is important to establish close links between the PV center and the national quality control laboratory (if there is one) as well as the pharmaceutical inspectorate unit. Both HCP and patients should be encouraged to report unexpected lack of effect of medicines to the PV center, thus contributing to the global efforts to document the extent of the problem of poor quality and counterfeited products and the harm to public health. Kenya, for example, has an impressive track record in detecting SSFFCs through its PV system and taking regulatory actions to remove them from the market [32].

Financing PV

PV is likely to be disadvantaged if the national PV center is hosted in a regulatory authority that is not fully funded by government grants but through fees for services to MAHs. PV is often co-organized with assessments of clinical trials or marketing authorization applications. As service fees for clinical trial and marketing authorization assessment often exist, but not for PV, the time of the PV specialist may be diverted into other activities for which the agency can charge, reducing the efficiency of the PV system development. Hopefully, the fee-based model for PV that has been introduced in the EU can be adapted elsewhere. However, it is important that governments also allocate dedicated funds for PV to ensure steady and sustainable support to PV in the country [33,34].

PV in PHPs

Traditionally, PHPs have focused on expanding access to treatment to achieve their goals of preventing or treating diseases in

populations. These programs rarely considered PV a priority until recently. This was obvious, for example, when WHO introduced the '3 by 5' strategy in 2003 to enable 3 million HIV-affected patients to receive treatment by 2005. The strategy did not include aspects of safety monitoring of individual patients on treatment. It was only when PHP managers realized that compliance with recommended treatment was threatened because of toxicity that patient safety and PV came into the picture. Patients were shifted to much more expensive second- or third-line therapy prematurely, threatening the budget and the success of the treatment programs [35,36]. In a similar manner, immunization programs have focused on population coverage and have not been very ambitious in systematically monitoring for Adverse Events Following Immunization (AEFI). Such AEFIs have received attention only when they undermined public confidence and threatened the success of the immunization program itself. In PHPs, there is thus a fundamental difference in attitude toward PV when compared with regular/everyday healthcare that integrates PV as part of routine care, with a focus on learning from every patient encounter, to improve treatment for future individual patients.

PHPs primarily need information on the risk profile of new medicines or vaccines being introduced to motivate recommendations and choice of products and instill trust and confidence in the population. They also need information about type and magnitude of serious adverse events that may occur after exposure and how they should be managed. In immunization programs, in particular, in which biological preparations sensitive to decomposition in unfavorable environments are used and distributed under difficult circumstances and administration of products occurs primarily through injections, focus is on events related to programmatic errors and their prevention.

PV methods for PHPs

Spontaneous reporting programs that are being introduced in resource-limited settings provide rather little support to meet the needs of PHP. With very low reporting rates and inherently selective and biased reporting, credible risk profiles and frequency estimates for new products will not be produced with spontaneous reporting. Although spontaneous reporting is always needed as a sensitive means of identifying rare and serious reactions among the exposed, additional methods are needed for safety profiling and estimates of rates of occurrence of adverse events. WHO has produced PV handbooks addressing the specific needs for PV in malaria, HIV/AIDS and tuberculosis [36–39] with a focus on cohort event monitoring and targeted spontaneous reporting [40]. Many LMIC countries, for example, Ghana, Nigeria, Tanzania, Kenya, Uganda and Zimbabwe have piloted these methods and have demonstrated their feasibility [41,42].

Monitoring AEFI

WHO handbooks for AEFI monitoring are also available and through the Global Vaccine Safety Initiative [43] and the Vaccine Safety Blueprint [44], WHO has made a major effort

recently to draw attention to vaccine PV. Unfortunately, there is still no global coordination of vaccine safety data to support the effective analysis of signals of new and serious vaccine-related problems. In many countries, there is little communication and data exchange between the national immunization program and the regulatory system responsible for PV in the country.

A growing awareness for PV

Global Health Initiatives and donors mentioned above have also recognized the need to support PV as a means of protecting the credibility of PHPs. An important step was taken by the GF when introducing PV as a requirement in the proposals for the 10th round of grant applications from countries. Collaboration between GF and WHO identified the minimum requirements for a functional PV system [14]. Support from the GF has allowed many health professionals to attend PV training courses organized by the WHO network and others resulting in good PV capacity in LMIC.

The BMGF initiated a safety surveillance working group that conducted a series of meetings in 2012 with the aim of developing a strategy to ensure that new vaccines and medicines that will be launched in resource-limited countries during the next decade will also be followed-up for post-marketing safety with appropriate PV methods. The proposed model envisages collaboration between governments, donors and industry organizations and the creation of a trust fund to remedy the present underfunding of post-marketing safety in resource-limited countries [45].

Building bridges

A major challenge for the further development of PV in PHP is to overcome the communication gap that often exists between medicine regulatory authorities, responsible for products safety and PV, and PHP managers. The lack of proper collaboration between these structures exists on international, national and local levels [37]. Recent joint PV activities in some countries, for example, Kenya and Uganda, are providing good collaboration models for the future [46].

PV in healthcare

The basis of PV in healthcare is the ethical principle of Hippocrates 'First, do no harm'. In other words, patients should not be harmed unnecessarily and treatment choices should be based on best current knowledge and evidence of benefit and harm. Such evidence is created from scientific studies and the experience of astute professionals and patients. PV is the system that provides the link between the observations and reports of HCPs and patients, and the analytical capacity and information resources of the designated center of the system. Efficient communication between the various parts of this system is essential for it to operate well for the benefit of patients. These principles are valid for all PV systems but are more challenging to implement and maintain in resource-limited countries.

Task-shifting

Because patient records are often absent or incomplete in resource-limited settings, ADR reports would need to be filled-in immediately, while the patient is present at the consultation, and cannot be extracted later, from patient records. The physician to patient ratio is generally very low in resource-limited countries, allowing little time for recording ADRs; the responsibility for filling out reporting forms could be 'task-shifted' to other HCPs, including nurses. However, the ultimate responsibility for the ADR reports should remain with the treating HCP.

Leveraging modern technology

Technological development in the past decade, particularly the widespread use of mobile phones, is rapidly changing the situation for the better. A majority of patients in most resource-limited countries have access to mobile phones [47]. Patients can be reached for active follow-up or for further information regarding their treatment. An SMS-based reporting system for ADRs has been established, for example, in Nigeria [48] and the technology is spreading rapidly.

Computers are rapidly becoming available in healthcare facilities. Not all of them are yet connected to the Internet but the potential for leap-frogging from a situation of no patient records to the most advanced electronic patient recording system is there and being explored [49]. Although access to broadband Internet requires greater infrastructure & investments, it is still spreading quite fast. The technological development is and will be a great opportunity for resource-limited countries to catch up and get access to electronic information sources, often available for free on the Internet, for example, the WHO HINARI system [50]. The next challenge is, like in all countries, to discern valid and reliable information from the unreliable.

Ethical incentives

The challenge for PV professionals is to offer sufficient incentives to HCP to spend time on ADR reporting and patient follow-up. Such incentives should primarily be related to professional performance, for example, allowing the HCP to provide better quality of care to patients, leading to better treatment outcome, patient confidence and professional growth. The PV system has to offer convenient access to information on the risk and benefit of treatment options that are considered relevant to the HCP. This is normally best done if the PV system is decentralized allowing direct and personal contacts between HCP and the PV professional [51].

PV in private sectors

Some resource-limited countries find it particularly difficult to engage private health facilities in PV activities. There is a common but false perception among managers of such institutions that high quality healthcare can be provided without any ADRs or medication errors occurring. Consequently, reporting adverse reactions or, even worse, reporting medication errors voluntarily would be tantamount to conceding lack of competence and inferior quality of healthcare. On the other hand, high quality

healthcare facilities run ambitious quality assurance programs to identify adverse reactions and potential or real medication errors and learn from them. It is known from numerous scientific studies in many different settings that at least 5% of hospital admissions are due to adverse reactions and approximately the same percentage of patients are affected by ADRs during their in-hospital stay [4,52,53]. If the healthcare institution does not have the ability to identify the ADRs, it is not quality conscious and has no ambition of improving its services for the benefit of patients. In a competitive healthcare environment, it ought to be an advantage to demonstrate the ability to identify, report and manage adverse reactions and medication errors. In many countries, private health facilities need to have a practice license from an accreditation body. Requirements for accreditation for healthcare facilities ought to include the presence of a quality assurance system ensuring the identification of adverse reaction and medication errors.

Traditional practitioners

Involving practitioners of traditional medicines in PV activities is another challenge in LMIC. For many of the traditional healers, their methods and remedies used are professional secrets. Moreover, the common perception in the general population is that natural remedies are, by their very nature, free from adverse reactions. The therapeutic remedies used in traditional medicine are also poorly characterized, which makes causality assessment and root cause analysis of adverse incidents very complicated. Some countries, for example, China and India, have very well-established systems for traditional medicines with separate official pharmacopoeias. In PR China, approximately 15–20% of collected ADR reports refer to effects of traditional medicines [54]. In India, the authority regulating the traditional systems of medicine, Ministry of Ayush, is organizing a separate PV program for traditional medicines.

PV in academia

Very few universities offer specific courses in PV or education covering the whole range of subjects relevant to PV. This is particularly true for resource-limited countries. As mentioned above, the WHO recognizes the need to support universities in developing curricula for undergraduate PV studies. To this end, the WHO established a WHO Collaborating Centre for Pharmacovigilance in Education and Patient Reporting in the Netherlands.

In some LMIC countries in which PV systems were introduced several years ago, there is now a demand from PV staff for competence development beyond the basic level. Post-graduate training in relevant subjects is not easily accessible in resource-limited countries and only a few universities in high-income countries are currently offering relevant places [55]. Also, access to fellowships is needed to support PhD projects for the many interested candidates. It is hoped that the comprehensive WHO-International Society of PV curriculum developed and published in 2014 covering all aspects of PV [56] would be useful in the continuing development of these practicing PV professionals.

Academic professors, for example, in clinical pharmacology, clinical pharmacy, internal medicine and other clinical specialties, are often engaged as expert advisors in national drug safety advisory committees. Through such engagements, they can also become involved in investigations related to specific medicine safety issues. Such routines add scientific rigor to analyses and also directly involve academic institutions in practical PV.

Outcome measurements

Most PV systems established in resource-limited countries are relatively young and cannot yet rely on nationally collected data to identify signals of medicine-related problems in their population. This is not surprising as the introduction of PV requires mobilization and change of mindset of a large number of HCPs and decision makers. This process took several decades in high-income countries where under-reporting is still a major problem [57]. Recent surveys have demonstrated major gaps and shortcomings in national PV programs in resource-limited countries, including the paucity of regulatory decisions based on local information [58–60]. As the market for newly introduced and expensive medicines in these countries are normally very small, their PV systems should focus on identifying preventable problems related to the use of well-established medicines used by many patients. Such problems might not be new in the sense of not having been described before, but their prevention would have the greatest impact on patient health.

WHO has recently developed a set of PV indicators to measure the status and development of PV systems in health facilities and countries [61]. These indicators will be important to identify gaps and the need for further investments in for example human resources or infrastructure. The efficiency of such investments could also be measured if the indicators are applied longitudinally.

Role of international and regional organizations

The WHO Program

WHO and its Program for International Drug Monitoring, established as a pilot in 1968, has played a pivotal role in stimulating and supporting PV in LMICs [62,63]. While policy, strategic development and coordination of the program are managed by WHO headquarters in Geneva, since 1978, the everyday technical operations have been handled by the WHO collaborating center for International Drug Monitoring in Uppsala, Sweden (UMC). UMC maintains the global ICSR database, VigiBase[®] that has at present 11 million ADR reports from 120 countries. Very few resource-limited countries joined the WHO program before the 1990s but, partly as a result of specific international PV training organized by UMC, WHO-HQ, and the other WHO collaborating centers, the number of LMICs establishing national PV centers has gradually increased (FIGURE 1). The UMC training courses in Sweden have reached more than 600 HCPs from over 100 countries. Many more have been trained in other parts of the world. Guidance documents and definitions issued by WHO and its Advisory Committee on the Safety of Medicinal Products (ACSOMP)

helped in supporting this development [64–66]. However, most of these guidance documents are in English, to the disadvantage of non-Anglophone countries.

Another key reason for successful expansion of the WHO program in LMIC is the annual meeting of representatives of national PV centers. These meetings, organized annually since 1978 in various member countries, bring together professionals from the most advanced and experienced centers as well as newcomers. Lectures, working group sessions and informal discussions led to significant mentoring, networking and sharing of expertise.

Recognizing the increasing demand for PV training and the need for local support, WHO established additional WHO collaborating centers in Ghana (2010) [67], Morocco (2012) [30] and, as mentioned above, the Netherlands (2013) [24]. Each of these new collaborating centers has its own specific role and mandate in PV capacity building. The Ghana center is focusing on training and supporting English speaking African countries and also maintains a very important resource repository, the PV toolkit [68]. It also coordinates the African Pharmacovigilance Consultants Network dubbed PVSF – PV sans Frontières. The aim of PVSF is to build a network of African PV experts living and working in Africa and coming from English, French and Portuguese speaking countries to ensure a steady and stable availability of PV experts on the continent. Through WHO, PVSF members meet more or less annually with each meeting seeing the addition of more experts to the team. The Moroccan collaborating center supports the French and Arabic speaking countries in Africa and the Eastern Mediterranean Region and also has a special focus on training in the monitoring of medication errors.

As the organization responsible for maintenance of the global WHO database, VigiBase, UMC has many functions beyond PV training. It helps national PV centers manage their data flow, both nationally and globally. It has developed an Internet based, ICH-E2b compatible, data management system, VigiFlow, that serves as a national database for more than 60 countries currently (FIGURE 2). All member countries of the WHO program have continuous and free access to all information in VigiBase through an interactive analytical tool, VigiLyze, that can produce listings, graphs and detailed case information from all countries. Another prominent function of the UMC is to perform signal analyses based on the global database and methodological research and development. Results of the signal analysis work are distributed to all the 149 participating countries (29 associate members not yet contributing to VigiBase) in the WHO program and also published in the WHO pharmaceuticals newsletter [69]. In 2015, UMC is focusing on applying their signal analysis methodology on data submitted from LMICs since the numbers have now become significant (FIGURE 3). The intention is to support the analytical capacity of countries with limited local facilities.

Other technical support organizations

The US Agency for International Development (USAID) has established the SIAPS program (Systems for Improved Access

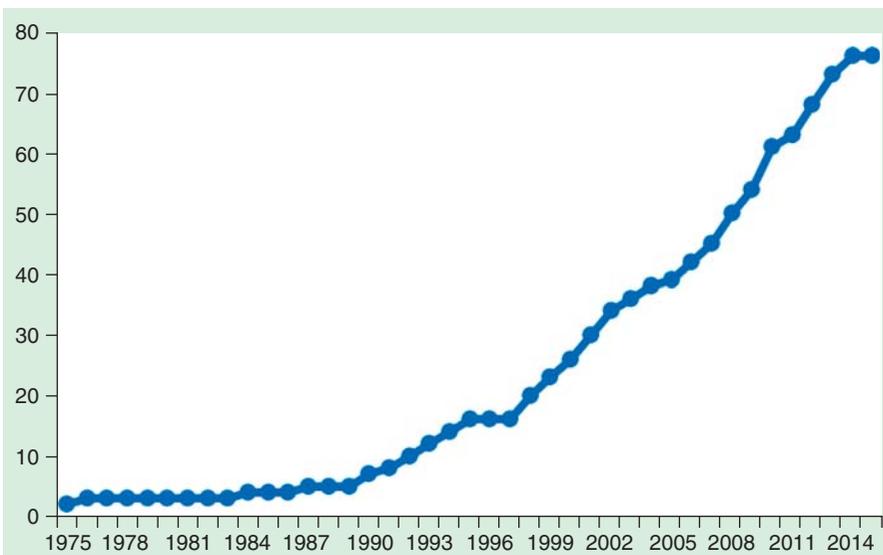


Figure 1. Number of LMIC countries becoming members of the WHO International Drug Monitoring Program over time.

to Pharmaceuticals and Services) including a component supporting PV in resource-limited countries. Management Sciences for Health is responsible for the implementation of these aspects in countries. Management Sciences for Health has engaged in capacity building and technical support for PV in a selected number of resource-limited countries. Analyses of the PV systems in Africa and five Asian countries have been performed [70,71] and a set of PV indicators developed [72].

Regional networks of regulatory authorities

In many parts of the world, regional networks have been created to support harmonization and regulatory convergence, including PV. Some of them have developed regional guidance documents to assist countries in adapting global best practice

guidelines to the local context. Such guidelines are available, for example, from the Pan American Health Organization (PAHO) through the PANDRH process [73]. In Africa, the New Partnership for African Development (NEPAD) has initiated the African Medicines Regulatory Harmonization (AMRH) Program, including the establishment of two regional centers for regulatory excellence (RCORE), in PV in Ghana and Kenya, the Ghana RCORE being a consortium including among others the national regulatory agencies of Ghana, Nigeria, Tanzania and Zimbabwe. The Asia Pacific Economic Cooperation (APEC) is working toward regulatory convergence among its member countries, including the PV area. APEC also engages in PV training and capacity building in collaboration with WHO.

Expert commentary

Not all LMICs have yet established national PV programs. In countries where such programs do exist, they are generally not underpinned by strong legal and regulatory support, hampering program implementation. PV is generally underfunded [45] and suffers from lack of trained professional staff [58] and high staff turnover. Activities focus on data collection and management rather than analysis but the young PV systems have generally not been efficient enough in collecting adequate safety information to support national regulatory decision making. In the absence of stringent regulatory requirements, it is very difficult to engage pharmaceutical companies, particularly local and generic companies, in PV activities. Existing mechanisms, such

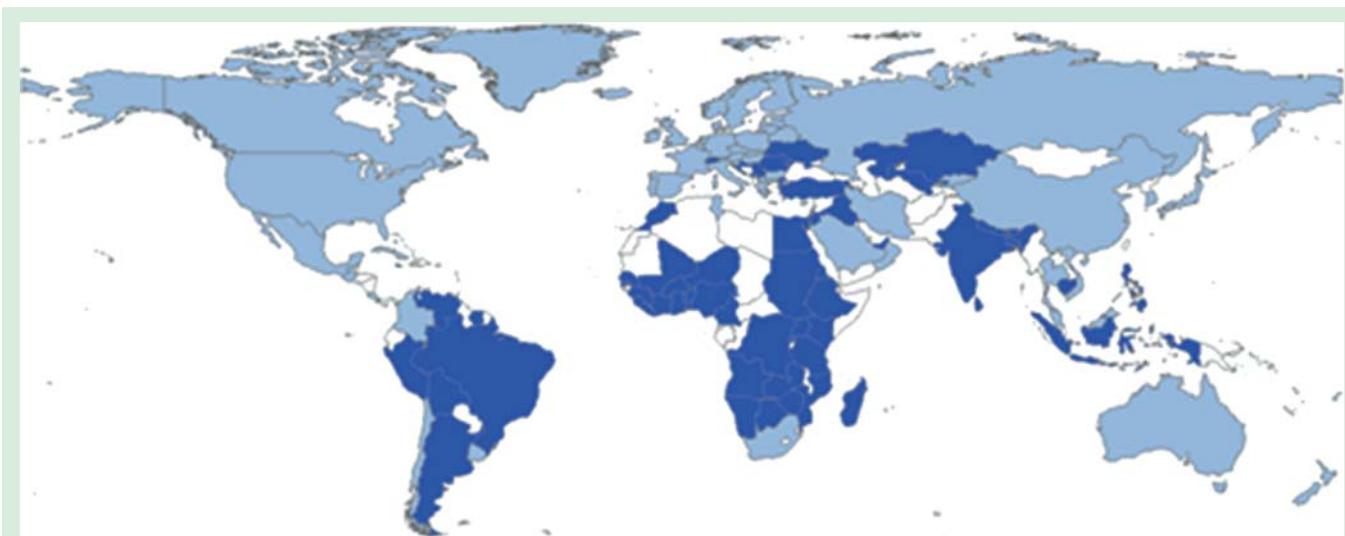


Figure 2. Sixty-five countries using VigiFlow December 2014 (in dark).

as the WHO prequalification programs should be better leveraged to address this challenge.

Politicians and healthcare decision makers need to be convinced of the urgent need for implementation of legal and regulatory instruments for PV to strengthen patient safety. Researchers need to assemble local evidence on the burden of drug-related harm from adverse reactions, medication errors and inadequate quality products in healthcare and their preventability.

Vertical PHPs are effective in preventing and combating priority diseases in resource-limited countries but they often also cause disruption of information exchange between different stakeholders in the healthcare system. A systematic follow up of adverse reactions and other problems associated with the use of medicines and vaccines in PHPs is frequently not done and even if safety data are collected they are often not shared with the drug regulatory authority and its PV program. WHO and national health authorities need to take measures to actively monitor the safety of new products being introduced in PHPs and systematically follow up safety issues over time through spontaneous reporting to capture trends of changes in the safety profile of products used. Efforts need to be coordinated between PHPs and the medicine regulatory system to ensure that countries do not run parallel systems for PV that would effectively keep the drug regulatory authority from making the well-informed benefit/risk assessments of marketed products that it is set up to do. National authorities must also give their own regulatory authorities the freedom to decide which products are approved for use in PHPs and restrict the use of products in PHPs if their risks far outweigh any perceived benefits.

National drug regulations should include a mandatory requirement for all organizations having the role of 'marketing authorization holders' to report adverse reactions and medication errors to the national PV system. While the direct effect of mandatory reporting for HCP on reporting rates has been disputed, the most important effect is to clarify that society considers it a professional obligation to follow up patients for possible unexpected effects from prescribed or administered medicines. Such effects should be documented and reported to allow for a systematic learning process. Mandatory reporting for healthcare providers gives a strong message that can be used in the promotion of PV to professionals.

One of the major shortcomings in modern PV is the failure to involve the training institutions for HCPs in PV capacity building. Physicians, dentists, nurses and pharmacists still leave their colleges for active service in healthcare without having had any systematic training on the burden of medicine-related harm and their role in reducing risks to patients and

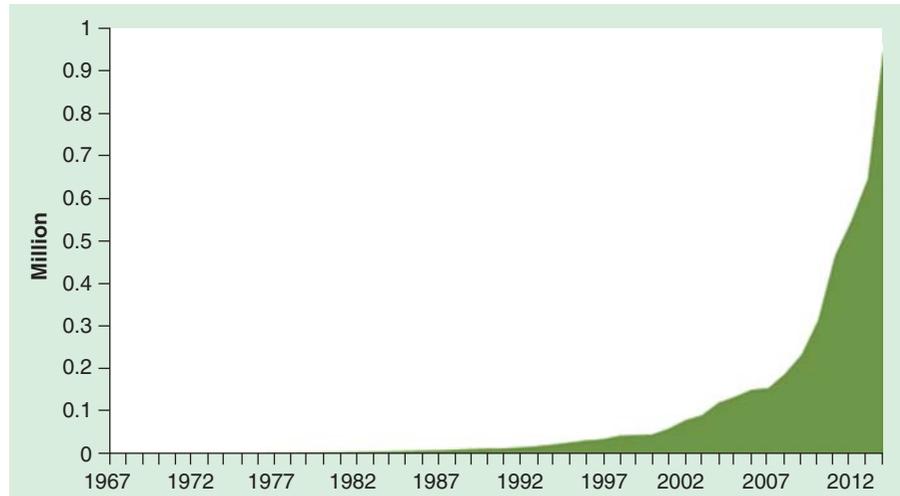


Figure 3. Number of ICSRs from LMICs included in WHO database, VigiBase, over time.

contributing to a systematic learning. The recent establishment of a WHO collaborating center for PV education in the Netherlands with one of its tasks to develop PV curricula for schools of HCPs is a late but very welcome initiative.

Recent development in information technology and wireless communication should be fully exploited to develop PV in LMICs. Patient follow-up through mobile phones is already used in some countries and electronic health records are slowly also being introduced in hospitals. Active monitoring systems and registries for pregnancy outcome follow-up also need to be established since many new medicines and vaccines are expected to be introduced in resource-limited countries without prior field testing in developed countries [45].

Although the direct participation of consumers and patients in PV has been controversial in the past, scientific evidence showing the unique value of patient observations to signal analysis is now in place [74,75]. In resource-limited countries with a low density of HCPs and a high level of self-medication, consumer participation in PV is particularly important. Active campaigns have to be launched to mobilize and motivate consumers in this regard [76].

Five-year view

By extrapolating current discussions and trends in the global PV arena, the following developments can be expected to take place in PV in resource-limited countries:

Regulatory strengthening & harmonization

Various regional networks of regulatory authorities in different parts of the world, with coordinating assistance of WHO, will have achieved tangible results in setting up model regulatory frameworks for PV for national implementation. A convergence toward requirements of ICH countries is anticipated but with due adaptation to the needs of the local settings. The ICH-E2b format for global exchange of ICSRs is likely to prevail. As a consequence of the strengthened legal provisions, generic

pharmaceutical companies will have to be engaged in PV planning and medicine safety follow-up. Sub-regional and even regional agencies are likely to move toward harmonization of requirements for drug regulation, including harmonized PV guidelines.

Public health programs

Donors having invested in the development of new vaccines and medicines for introduction in PHPs will create partnerships with national PHPs and the global pharmaceutical industry to ensure that new product launches are accompanied by active safety monitoring and continuous safety follow-up. Such joint investments in PV will ensure safe product introductions for appropriate populations and immediate management of unexpected safety concerns. Safety data collected will be shared with national PV centers operating under the framework of medicines regulatory authorities and will also be submitted to the WHO ICSR database, VigiBase, for optimal generation and analysis of signals.

Consumer involvement & technological development

PV needs to engage consumers and civil society groups in a dialog since a comparatively high proportion of medicine use is through self-medication in resource-limited countries. This process is facilitated by the rapidly growing access to mobile phones and information technology among wide sectors in society, fundamentally changing conditions for safety data

collection and communication with consumers. Internet and social media will be tapped as sources for consumer concerns. Introduction of electronic health records in healthcare and the establishment of pregnancy and disease or drug registries will allow longitudinal follow-up of individuals exposed to medicines and other health technologies including vaccines.

Human resource development

Expansion of PV activities and absorption of investments in LMICs can only be achieved if sufficient number of HCPs receives relevant systematic training in PV methodology, data analysis, and communications. WHO and its network of collaborating centers are expanding its capacity building activities to meet these needs together with its partners. Current limited efforts to engage academic institutions in resource-limited countries in PV education and training must expand, however. HCPs must realize the importance of PV in achieving optimal medicine treatment strategies. PV and patient safety will slowly grow into a career opportunity for HCPs in resource-limited countries.

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Key issues

- PV programs in most low- and middle-income countries (LMICs) are young, underfunded and not underpinned by strong legal or regulatory provisions. Stronger regulations are needed to engage local industry and healthcare professionals. Principles of good governance need to be applied for monitoring and enforcement of pharmacovigilance (PV) regulations.
- Local scientific evidence on the burden of medicine-related harm and their preventability needs to be created.
- Very few PV systems in LMICs currently have the capacity to collect sufficient and relevant local safety information to inform, and the analytical competence to carry out independent benefit/harm assessments.
- Public health programs need to urgently engage in PV, particularly active methods of patient follow-up, since new medicines and vaccines not introduced in the developed world, are being launched.
- Recent technological development offers new opportunities for collecting safety information from all sectors in society.
- Signal analysis in LMIC should focus on identifying high-burden preventable drug-related problems, rather than problems that have never been described before.
- Academic institutions need to be engaged in providing undergraduate PV training, ensuring that all new healthcare professionals know their role in documenting, reporting and learning from experience of medicine-related harm, including medication errors.
- As LMICs generally have a high level of self-treatment, active campaigns should be undertaken to engage the public in the process of reporting and learning about medicine-related problems.

References

Papers of special note have been highlighted as:

- of interest
 - of considerable interest
1. WHO Technical Reports No 498. International drug monitoring: the role of national centres. World Health Organization; Geneva: 1972
 2. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of adverse drug reactions. Oxford University Press, Oxford; 1977. p. 44
 3. Winterstein AG, Sauer BC, Hepler CD, Poole C. Preventable drug-related hospital admissions. *Ann Pharmacother* 2002; 36(7-8):1238-48
 4. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions – a meta-analysis. *PLoS One* 2012;7(3):e33236
 - **An extensive review of the literature on preventable medicine-related harm.**
 5. Guidelines for the development of measures to combat counterfeit medicines. WHO, Geneva; 1999. Available from: www.who.int/medicines/publications/counterfeitguidelines/en/
 6. The importance of pharmacovigilance. WHO, Geneva; 2002. Available from: <http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf>
 7. The Global Fund. Available from: www.theglobalfund.org/en/ [Last accessed 4 February 2015]
 8. UNITAID. Available from: www.unitaid.org/ [Last accessed 4 February 2015]
 9. UNICEF. Available from: www.unicef.org/ [Last accessed 4 February 2015]
 10. Gavi. Available from: www.gavi.org/about/ [Last accessed 4 February 2015]
 11. PEPFAR. Available from: www.pepfar.gov/ [Last accessed 4 February 2015]
 12. Bill & Melinda Gates Foundation. Available from: www.gatesfoundation.org/ [Last accessed 4 February 2015]
 13. Dodo A. WAHO and drug safety. *Uppsala Rep* 2010;50:16
 14. Minimum Requirements for a Functional Pharmacovigilance System. WHO, Geneva. Available from: www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf?ua=1 [Last accessed 4 February 2015]
 - **A concise description of the key functions of a national pharmacovigilance (PV) system and the basic premises needed to carry out those functions.**
 15. Osakwe A. Nigeria adopts national policy. *Uppsala Reports* 61, April 2013, Uppsala Monitoring Centre. Available from: <http://who-umc.org/graphics/27578.pdf> [Last accessed 4 February 2015]
 16. Eritrean National Pharmacovigilance Policy, State of Eritrea. Ministry of Health; Asmara: 2014
 17. FDA Philippines. Available from: www.fda.gov.ph/issuances/153551-administrative-order-no-2011-0009 [Last accessed 4 February 2015]
 18. Assessment of medicines regulatory systems in sub-Saharan African countries, An overview of findings from 26 assessment reports. WHO; Geneva: 2010
 19. Patel KJ, Kedia MS, Bajpai D, et al. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: a prospective study. *BMC Clin Pharmacol* 2007;7:8
 - **Illustrates how to study basic parameters demonstrating the burden of medicine-related disease in healthcare facilities.**
 20. Benkirane R, Pariente A, Achour S, et al. Prevalence and preventability of adverse drug events in a teaching hospital: a cross-sectional study. *Eastern Mediterranean Health J* 2009;15:1145-55
 21. Gyllensten H, Jönsson AK, Rehnberg C, Carlsten A. How are the costs of drug-related morbidity measured? A systematic literature review. *Drug Saf* 2012; doi: 10.2165/11597090-000000000-00000 0114-5916/12/0000-0000/\$49.95/0
 - **A comprehensive overview of methods used to study economic burden of medicine-related harm. Many useful references.**
 22. Biswas P. Pharmacovigilance in Asia. *J Pharmacol Pharmacother* 2013;4:7-19
 23. Zhang L, Wong LYL, He Y, Wong ICK. Pharmacovigilance in China: current situation, successes and challenges. *Drug Saf* 2014;37(10):765-70
 24. Available from: www.lareb.nl/whocc [Last accessed 7 February 2015]
 25. Dollen MZ. Pharmacovigilance Legislation: The impact of what is happening in Europe. *Ther Innov Regul Sci* 2014;48: 190-9
 26. Good Pharmacovigilance Practices. Available from: [www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp)
 - document_listing_000345.jsp [Last accessed 7 February 2015]
 - **Provides guidelines for all the XVI modules of the EU good pharmacovigilance practices regulations implemented from 2012.**
 27. Anonymous. European Pharmacovigilance: increasingly outsourced to drug Companies. *Prescrire International* 2014;23:302-7
 28. Pharmacovigilance guidelines. Available from: www.who-umc.org/DynPage.aspx?id=127878&mn1=7347&mn2=7252&mn3=7253&mn4=7745 [Last accessed 16 March 2015]
 29. Pharmacovigilance guidelines. Available from: www.who-umc.org/DynPage.aspx?id=97223&mn1=7347&mn2=7252&mn3=7254 [Last accessed 17 March 2015]
 30. Centre Anti Poison et de pharmacovigilance du Maroc. Available from: www.capm.ma/index.php [Last accessed 7 February 2015]
 31. Wilbur K. Pharmacovigilance in the Middle East; A survey of 13 Arabic-speaking countries. *Drug Saf* 2013;36:25-30
 32. PPB Pharmacovigilance Newsletter, December 2012. http://pharmacyboardkenya.org/?page_id=442 [Last accessed 7 February 2015]
 33. Pirmohamed M, Atuah KN, Dodo AN, Winstanely P. Pharmacovigilance in developing countries; Requires collaboration between stakeholders to develop novel models of funding. *BMJ* 2007;335:462
 34. Babigumira JB, Stergachis A, Choi HL, et al. A framework for assessing the economic value of pharmacovigilance in low- and middle-income countries. *Drug Saf* 2014;doi: 10.1007/s40264-014-014
 35. Available from: www.who.int/3by5/progressreportJune2005/en/ [Last accessed 8 May 2015]
 36. A practical handbook on the pharmacovigilance of antiretroviral medicines. WHO, Geneva 2009. Available from: www.who.int/hiv/pub/pharmacovigilance/handbook/en/ [Last accessed 8 May 2015]
 37. The Safety of Medicines in Public Health Programmes: Pharmacovigilance an essential tool. WHO; Geneva: 2006
 38. A practical Handbook on the Pharmacovigilance of Antimalarial Medicines. WHO; Geneva: 2009
 39. A practical Handbook on the Pharmacovigilance of medicines used in the treatment of tuberculosis. WHO; Geneva: 2012

40. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug Saf* 2013;36:75-81
- **An easy-to-read overview of recommended PV methods for public health programs.**
41. Bassi PU, Osakwe AI, Isah A, et al. Safety of Artemisinin-Based Combination Therapies in Nigeria: A Cohort Event Monitoring Study. *Drug Saf* 2013;36:747-56
42. Dodoo ANO, Fogg C, Nartey ET, et al. Profile of Adverse Events in Patients Receiving Treatment for Malaria in Urban Ghana: A Cohort-Event Monitoring Study. *Drug Saf* 2014;37:433-48
43. Global Manual on Surveillance of Adverse Events Following Immunization. Available from: www.who.int/vaccine_safety/publications/aeft_surveillance/en/ [Last accessed 7 February 2015]
44. Available from: www.who.int/vaccine_safety/en/ [Last accessed 7 February 2015]
45. Available from: https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%2011%2019%2013_designed.pdf [Last accessed 7 February 2015]
46. Ndagije H, Nambasa V, Namagala E, et al. Targeted Spontaneous Reporting of suspected renal toxicity in patients undergoing Highly Active Anti-Retroviral Therapy in two public health facilities in Uganda. *Drug Saf* 2015;38(4):395-408
47. Sharon Pandian S, Kang G. The Antenatal and Infant Monitoring System: Promoting AEFI Reporting in Difficult Environments. An innovative approach using interactive voice response (IVR) technology. *GVSI Bulletin* 2015;7:3
48. Jajere F. Rapid consumer reports. *Uppsala Reports* 2014;65:16
49. who-pvafrica.org/index.php/med-spina [Last accessed 8 March 2015]
50. Available from: www.who.int/hinari/about/en/ [Last accessed 7 February 2015]
51. Moore N, Biour M, Paux G, et al. Adverse drug reaction monitoring: doing it the French way. *Lancet* 1985;2(8463):1056-8
52. Commission of the European Communities, Brussels 2008. Available from: [www.europarl.europa.eu/RegData/docs_autres_institutions/commission_europeenne/sec/2008/2671/COM_SEC\(2008\)2671_EN.pdf](http://www.europarl.europa.eu/RegData/docs_autres_institutions/commission_europeenne/sec/2008/2671/COM_SEC(2008)2671_EN.pdf) [Last accessed 7 February 2015]
53. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother* 2013;4:73-7
54. China Food and Drug Administration. 2012 Annual Report of National Adverse Drug Reaction Monitoring, Beijing. 2013;4
55. Available from: www.pharmaceuticalpolicy.nl/PhD%20Program.html [Last accessed 8 March 2015]
56. Beckmann J, Hagemann U, Bahri P, et al. Teaching Pharmacovigilance: the WHO-ISO P Core Elements of a Comprehensive Modular Curriculum. *Drug Saf* 2014;37(10):743-59
- **Attempts to cover all topics relevant to any training in PV.**
57. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions - a systematic review. *Drug Saf* 2006;29(5):385-96
58. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries a questionnaire-based analysis. *Drug Saf* 2010;33(8):689-703
- **A broad survey of strengths and weaknesses of PV systems in LMICs.**
59. Isah AO, Pal SN, Olsson S, et al. Specific features of medicines safety and pharmacovigilance in Africa. *Therap Adv Drug Saf* 2012;3(1):25-34
60. Vadiya S.S, Guo J.J, Heaton P, Steinbuch M. Overview and comparison of postmarketing drug safety surveillance in selected developing and well-developed Countries *Drug. Inf J* 2010;44:519-33
61. Anonymous. WHO Pharmacovigilance Indicators. WHO; Geneva: 2015; In press
62. Olsson S. The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts. *Drug Saf* 1998;19:1-10
63. Pal S, Dodoo A, Mantel A, Olsson S. Pharmacovigilance and Safety of Medicines, In The World Medicines Situation Report, WHO, Geneva. 2011. Available from: <http://apps.who.int/medicinedocs/documents/s18771en/s18771en.pdf> [Last accessed 9 March 2015]
- **The most comprehensive overview available of the PV situation in the world.**
64. WHO Programme Members. Available from: www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442 [Last accessed 7 March 2015]
65. Safety Monitoring of Medicinal Products: Guidelines for setting up and running a pharmacovigilance Centre. Uppsala Monitoring Centre; Uppsala: 2000
66. WHO Guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. WHO; Geneva: 2004
67. Available from: <http://WHO-pvafrica.org> [Last accessed 8 March 2015]
68. Available from: <http://pvtoolkit.org> [Last accessed 7 February 2015]
- **A very rich source of practical information relating to the implementation and practice of PV. Includes specific chapters for public health programs.**
69. Available from: www.who.int/medicines/publications/newsletter/en/ [Last accessed 7 February 2015]
70. Comprehensive Assessment of Pharmacovigilance Systems and their Performance in Sub-Saharan Africa 2012. Available from: <http://siapsprogram.org/publication/comprehensive-assessment-of-pharmacovigilance-systems-and-their-performance-in-sub-saharan-africa/> [Last accessed 7 February 2015]
71. Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries. 2014. Available from: <http://siapsprogram.org/publication/comparative-analysis-of-pharmacovigilance-systems-in-five-asian-countries/>. [Last accessed 7 February 2015]
72. Strengthening Pharmaceuticals Systems (SPS) Programme 2009. Indicator –Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the U.S. Agency for International Development by the SPS Programme. Arlington, VA: Management Sciences for Health; 2009
73. Available from: www.paho.org/hq/index.php?option=com_content&view=article&id=1592&Itemid=40147 [Last accessed 8 March 2015]
74. van Hunsel FPAM. The contribution of direct patient reporting to pharmacovigilance. thesis Groningen: Rijksuniversiteit Groningen; 2011
75. Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011;15:20
76. Hartigan-Go K. Empowering consumers as contributors for health product safety: lessons from the Philippines. *Drug Saf* 2015;38(4):329-35