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Why is the Safety of Medicines Important for Resilient Health Systems?

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Do No Harm Synthesis Report

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A Synthesis Report

Why Is the Safety of Medicines Important for Resilient Health Systems?

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Abstract

- This report discusses the importance of pharmacovigilance (PV) in contributing to building up resilient health systems. It is based on and summarizes the findings of a review of available literature on the topic and relevant case studies focusing on a set of country and regional experiences.
- Although indispensable in improving health outcomes, the administration and use of medicines may produce adverse reactions, requiring continuous monitoring to ensure that the benefits outweigh the risks. PV, which involves the systematic detection, reporting, assessment, understanding, and prevention of adverse drug reactions (ADRs), is an essential public health function, but it is often overlooked. The goals of PV are to improve patient safety through the timely detection of previously unknown ADRs that are revealed to be associated with medicines during post marketing surveillance; promote the safe use of medication; enhance public health through the appropriate use of medication; contribute to the assessment of benefits, harm, effectiveness, and risks of medicines; and encourage the safe, rational, more effective, and cost-effective use of drugs. The recent Covid-19 pandemic has highlighted the value of PV in building resilient health systems that respond well during a public health crisis and in normal times.
- The review suggests that successful PV programs are built on three essential pillars: statutory provisions that establish standards for PV centers and programs, well-trained health professionals and associated stakeholders, and engaged PV reporters using effective reporting systems. These pillars allow PV programs to be effective in three core activities: reporting adverse drug events (ADEs) and identifying signals, determining threats through a benefit-risk balance analysis, and taking appropriate actions. This is in addition to supporting various functions of a health system, such as national drug policy and regulation, the delivery of medical care, specific disease control programs, increasing the trust of the general public in the system, and promoting eco-PV.
- Aided by emerging opportunities for development through automation and machine learning, PV programs show immense potential to enhance the monitoring of patient safety and improve the use of medicines. The report offers policy considerations for countries and international partners in building PV capacity as an essential public function of a health system.

“是药三分毒” (shì yào sān fēn dú) “
“All medicines have three parts of poison”

Chinese proverb
Implies that every medicine, no matter how effective it may be, can also have harmful side effects if not used properly or if it is taken in excess.

“Does a drug work? Does an intervention that everyone’s using already work? We can’t tell that without having some sort of systematically collected data. And I want to emphasize the ‘systematically’ part.”

Eric Rubin, Perspective Intention to Treat, “Lessons for a Pandemic,”
New England Journal of Medicine, June 1, 2023

Clinical trials cannot reflect the experience in larger populations and in different geographical regions

1. Introduction

Medicines, vaccines, and other essential health technologies are among the main therapeutic tools used by health professionals for the prevention, detection, and treatment of diseases. Although indispensable for improving health outcomes, medicine and vaccine administration and usage can produce adverse effects, requiring continuous monitoring to ensure that the benefits outweigh the risks.

Drug safety monitoring, also known as pharmacovigilance (PV), takes advantage of the longer follow-up periods after the clinical trials and market approval, when patients with a wider range of characteristics and in different geographical locations are using the medicines and vaccines, as a valuable opportunity to identify, describe, quantify, and, if necessary, reduce any adverse effects to the medications that might be revealed. In practice, this means establishing well-organized PV or monitoring arrangements within a health system for the identification, reporting, and assessment of the risks associated with the use of medicines. These processes involve experienced personnel, policy makers, health care professionals, manufacturers, and citizens actively participate.

This report is based on and summarizes the findings of a review of available literature on the topic and relevant case studies focusing on a set of country and regional experiences. The goal of this report is to provide a comprehensive picture of the role of PV in health systems, discuss the building blocks of a well-structured and functional PV system, and highlight the value of drug safety monitoring in building resilience in health systems post-pandemic. The report concludes by presenting policy considerations for countries and international partners on building PV capacity as an essential public health service in an effective system.

2. Why Drug Safety Matters?

2.1 Safety Is an Integral Part of Health Care Quality

The administration and use of medicines entail both benefits and risks. As explained by the US Food and Drug Administration, the benefits of medicines are the helpful effects a person experiences in using the medicines, such as lowering blood pressure, curing infection, or relieving pain (FDA 2018). The risks of medicines revolve around the chance that an unwanted or unexpected reaction could occur to a person who uses the medicine, such as the possibility of damage to body tissues or organ functions or a harmful interaction between the medicine and a food, beverage, dietary supplement (including vitamins and herbals), or other medicine. Any combination of these products could increase the chances of adverse pharmacological interactions, the chance that the medicine may not work as expected, or the possibility that the medicine may cause additional problems.

Some of the risks of medicines are manifested as adverse drug events (ADEs), which are harms that may occur while patients are taking a medicine, irrespective of whether the medicine is suspected as the cause. However, some ADEs may be causally related to medicines. These are referred to as adverse drug reactions (ADRs). PV monitors ADEs and, by analyzing reports, identifies ADRs. ADRs are unwanted or harmful reactions that are experienced following the administration of a medicine or a combination of medicines under normal conditions of use and that are suspected to be related to or caused by the medicines. ADRs represent a significant challenge to health systems, particularly because of the increasing complexity of therapeutics, aging populations, and multiple comorbidities.

Medication safety monitoring is an essential component of continuous quality improvement in health care, which involves a progressive, incremental improvement in processes, safety, and patient care (Marquez 2020). ADRs can occur in any setting, such as outpatient facilities, hospitals, nursing homes, and patient households. The underreporting of ADRs is a critical problem everywhere.

2.2 The Burden of Adverse Drug Reactions

Although most ADRs are mild, serious ADRs sometimes lead to (a) clinical complications among patients who are already frail, (b) longer hospital stays or longer periods away from work to receive additional treatments to manage the ADRs, (c) rising health care costs, and (d) the occasional death of the patient. The results of various studies suggest that ADRs are common causes of hospital admission and, in some cases, can be serious or fatal (Bénard-Laribière et al. 2015; Brvar et al. 2009).

A retrospective analysis of *VigiBase*, the World Health Organization (WHO) PV database, investigated fatal ADRs registered between January 1, 2010, and December 31, 2019, among adult men and women patients and reported by physicians (Montastruc et al. 2021).[1] It provided evidence on the extent of reported fatal ADRs and the main drugs involved in these fatal ADRs. Because *VigiBase* is the largest PV database in the world, it offers unique opportunities to cover the global population, factoring in differences in medical practice and cultural characteristics to make comparisons and generalizing the results to the whole world and not only to a single part of the world or a single country. A sample of 3,250,967 ADRs recorded in *VigiBase* were included in the study, according to the selection criteria. Among these, 43,685 (1.34

[1] See "About *VigiBase*," Uppsala Monitoring Center, Uppsala, Sweden, https://who-umc.org/vigibase/.

percent) were defined as fatal. More than 50 percent of the reports concerned males, mostly patients ages 45–64, from the Americas, followed by Europe. The study found that the shares of fatal ADRs registered in *VigiBase* were stable (around 10 percent–13 percent each year) except in 2010, 2012, and 2013, when lower values were observed. The most frequent suspected pharmacological groups were antineoplastic/immunomodulating, neurological, and cardiovascular drugs.[2] A recent multiyear study in New Zealand reported that opioids, antidepressants, antipsychotics, and hypnotic-anxiolytics were the drugs causing most fatalities (Fountain et al. 2020).

The burden of ADRs on health systems has been estimated using service utilization and health care cost metrics. For example, the prevalence of hospital emergency department visits for ADRs in the United States was estimated at 4 per 1,000 visits in 2013 and 2014; commonly used medicines, such as anticoagulants, antibiotics, medications to treat type 1 and type 2 diabetes, and opioid analgesics, were the most common drug classes implicated (Shehab et al. 2016). Recent work at the United States Centers for Disease Control and Prevention has estimated that more than 1 million individuals are seen in hospital emergency departments for ADRs each year in the United States, and more than one-quarter of these patients must be hospitalized for further treatment.[3]

Similarly, a European Commission report documented that 3 percent–10 percent of hospital admissions between 2012 and 2014 were estimated to have been associated with ADRs, totaling about €2.5 million–€8.4 million annually, and 2.1 percent–6.5 percent of hospitalized patients experienced an ADR, corresponding to €1.8 million–€5.5 million annually (EC 2016). In addition, at least one ADR onset during hospitalization was associated with a median prolongation in a hospital stay of four days, which is similar to the conclusion of another study (Nobili et al. 2011).

The findings of a recent study in the Republic of Korea that compares health care costs six months before and after the ADRs show that (a) tertiary emergency department visits associated with ADRs increased the associated direct medical costs by 26.1 percent; (b) after emergency department visits for ADRs, the inpatient costs increased by 28.0 percent, and the outpatient costs by 7.0 percent; and (c) copayments for patients and noninsurance costs rose by 56.0 percent and 41.3 percent, respectively (Lee et al. 2020). The study also estimates that 16.6 percent of the ADR cases were preventable, which indicates that preventing these ADRs would allow cost savings of up to 19.9 percent of all ADR-induced costs.

Another study provides estimates on the costs of drug-symptom pairs for severe outpatient ADRs that resulted in or contributed to hospitalizations in the United States (Aspinall et al. 2022). In the study, the costs of ADRs by drug-ADR symptom–coded pairs using Medical Dictionary for Regulatory Activities (MedDRA PT) terms were summarized, and the costs were adjusted to 2018 US dollars.[4] The most frequently reported drug-symptom pairs were lisinopril-angioedema (7.9 percent of the reports), warfarin-hemorrhage (6.1 percent), and warfarin–gastrointestinal hemorrhage (4.8 percent). Hydrochlorothiazide/lisinopril-angioedema exhibited the lowest median cost during fiscal years 2014 through 2018, at US$6,951 (interquartile range, US$4,720–US$10,510). Enoxaparin-hemorrhage exhibited the highest median cost, at US$29,535 (interquartile range, US$21,231–US$44,236). The results of the study also illustrate the potential cost avoidance of interventions to reduce ADRs (for instance, the use of a newly developed direct oral anticoagulants dashboard).

[2] In the anatomical therapeutic chemical classification system, active substances are divided into various groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. For details, see ACT (Anatomical Therapeutic Chemical Classification) (dashboard), World Health Organization Collaborating Center for Drug Statistics Methodology, Department of Drug Statistics, Norwegian Institute of Public Health, Oslo, https://www.who.int/tools/atc-ddd-toolkit/atc-classification.

[3] See Medication Safety Program (dashboard), Centers for Disease Control and Prevention, Atlanta, https://www.cdc.gov/medicationsafety/index.html.

[4] MedDRA is a rich and highly specific standardized medical terminology developed to facilitate the sharing of regulatory information internationally on medical products used by humans. It is used for registration, documentation, and the safety monitoring of medical products both before and after the products have been authorized for sale. Products covered by MedDRA include pharmaceuticals, vaccines, and drug-device combination products. For details, see MedDRA (Medical Dictionary for Regulatory Activities) (dashboard), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, https://www.ich.org/page/meddra.

3. What Is Pharmacovigilance?

3.1 The Objective and Scope of PV

The etymological roots of the word pharmacovigilance are as follows: pharmakon (Greek: φαρμακο-, φάρμακον) = medicinal substance, and vigilia (Latin) = to keep watch. The WHO (2002, 7) defines PV as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems." PV is thus a system to monitor the safety and effectiveness of medicines and other pharmaceutical products and involving all entities and resources that protect the public from medicine-related harm, whether in personal health care or in public health services (Shrestha et al. 2021).

Effective PV requires that the collection and assessment of individual case safety reports be routinely undertaken for all medicinal products to identify previously known or unknown ADRs, especially those that may be serious or fatal.

Undertaking these activities is particularly important in the first decade after marketing authorization of a new drug, as they may help, for example, identify complications from drug administration and use that were unknown before commercialization (Sardella et al. 2021). While there is general acceptance that the safety profile of older medicines, such as generic drugs, is already well established and unknown adverse reactions are unlikely to occur, these medicines may generate new risks associated with failures in control quality in the various phases of the manufacturing and distribution of pharmaceutical products (Sardella et al. 2021; SPS 2009b).

It has therefore been suggested that, to detect safety hazards associated with the use of newly approved medicines and to prevent the development of new complications that may arise because of the poor quality of older medicines, the manufacturing and pharmacovigilance quality systems be fully integrated in the medicine life cycle (Sardella et al. 2021).

The aim of monitoring the quality of available pharmaceutical products is to identify products that are defective or deteriorated because of poor manufacturing practices (for instance, the inadequate control of quality defects in one or multiple batches or inadequate impact assessment of changes or variations in manufacturing or quality control testing); inadequate storage and distribution processes; inadequate control over distribution channels, including introducing in the supply chain counterfeit or falsified products or medicines that have lost their potency during storage at high temperatures.

Monitoring the drug safety hazards associated with medication errors is also critical in PV. Medication errors are defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer."[5] They may result from faulty systems, processes, or conditions that lead people to make mistakes or fail to prevent mistakes. (For instance, problems can result from illegible handwriting, the use of faulty abbreviations, overlooked interactions with other medicines, oral miscommunication, and sound-alike or look-alike products.) An ADR is a harmful response that may be fatal, life-threatening, significantly disabling, or sometimes permanent and that is caused by the medicine after it was given to the patient in the recommended manner (dose, frequency, route, administration technique) (UMC 2000).

The overall goal of PV is to improve patient care and safety through the use of any kind of medication;

[5] About Medication Errors (dashboard), National Coordinating Council for Medication Error Reporting and Prevention, United States Pharmacopeial Convention, Rockville, MD, https://www.nccmerp.org/about-medication-errors.

enhance public health and safety in the use of medications; contribute to the assessment of the benefits, harm, effectiveness, and risks of medicines; and encourage the safe, rational, more effective, and cost-effective use of drugs. This is accomplished through the efficient and timely collection and assessment of ADEs and the identification of ADRs among these events. The reporting of adverse reactions after the use of a drug or vaccine contributes to (a) inform decision-making in a health system, (b) update and supply guidance to health providers, (c) help address public safety concerns about new medicines and vaccines, and (d) stimulate prompt policy and regulatory actions.

Building the capacity across countries and regions to conduct thorough surveillance of the use of all me dicines and vaccines is a critical public good investment to ensure that these drugs work correctly and that their health benefits outweigh the known risks.

The accumulated experience during the COVID-19 pandemic clearly illustrates the important role that PV can play in a health system not only in normal times, but also during public health crises (box 1).

Box One

A Lesson of the COVID-19 Pandemic

The pandemic experience has shown that a robust PV system can play an important role in two ways: (a) ensuring the detection, assessment, understanding, and prevention of adverse effects or any vaccine or medicine-related problem that may only emerge after the approval of any new product and (b) informing governments and other stakeholders about the safety of these products to guide policy making and regulatory action, and to communicate risks properly and promote the take-up of marketed vaccines and medicines.

While vaccination against COVID-19 provided clear public health benefits, it also carried potential risks. For example, the European Medicines Agency (EMA), after reviewing safety signals associated with the administration of the AstraZeneca COVID-19 vaccine in some European Union (EU) countries in early 2021, was able to advise governments to resume vaccination based on the results of its review and communicate to the population that the benefits of the AstraZeneca vaccine in preventing COVID-19, with the associated risk of hospitalization and death, outweighed the risks of reported adverse effects.

EMA work also helped inform policy making in countries outside Europe. For example, on March 16, 2021, EMA stated that the benefits of the AstraZeneca vaccine continued to outweigh the risks based on a review of all reports of thromboembolic events among 5 million people receiving the vaccine. Subsequently, the WHO issued a statement, on March 17, 2021, to reiterate the EMA position, and the African Centers for Disease Control and Prevention, in a statement issued on March 19, 2021, recommended that African Union member states continue to roll out this vaccine as part of their vaccination campaigns.

The work of the EMA has been crucial in informing not only governments, but also stakeholders on the benefits and risks of marketed medicines. If not communicated well, reported adverse drug effects have the potential to undermine public confidence in vaccines and other medicines and in government actions in general.

Source: Wang, Marquez, and Figueras 2022.

3.2 Core PV Activities

Different actors and mandates are involved in monitoring and the responsibility for the safety of medicines and vaccines across the three core PV activities: (a) reporting on adverse events and identifying ADRs, (b) detecting significant safety issues and identifying changes in achieving the balance between the benefits and risks of a given medicine, and (c) taking appropriate actions in a timely manner if necessary, for instance, improving safety labels, altering prescription practices and guidelines, changing benefit packages, educating service providers, communicating with patients and to the general public, and withdrawing a proven harmful medicine from the market (table 1).

Table 1 Activities, Actors, Mandates, and Incentives in Spontaneous ADR Reporting

Activities	Actors	Mandates and incentives
Reporting adverse events	Front-line health workers (physicians, nurses, pharmacists, and others)	In general, reporting is not part of the mandatory responsibilities of health workers; often there is little incentive for them to report. Underreporting is a common hurdle of safety monitoring programs. But other reporting systems are acceptable, such as the compulsory reporting of certain infectious diseases.
	Consumers (patients, family members, patient associations)	Empowerment: taking part in the decisions and follow-up on health care issues
	Manufacturers (pharmaceutical companies)	Among manufacturers, there are often legal requirements to report. A large number of reports are collected. Partial reports sometimes lack basic information.
Detecting significant safety issues and identifying changes in the balance of benefits and risks in a given medicine	Public health professionals who code and analyze ADR reports, conduct research to amplify signals, and, if needed, plan other comprehensive observational studies	Often full-time jobs or institutions with dedicated responsibilities and mandates for conducting related activities; PV centers located at or in close collaboration with university departments and public hospitals have an active role in this research.
Taking appropriate actions	National and local health authorities, for example, ministries of health, local health councils	Policy changes and decision-making
	Regulatory authorities with a role in translating meaningful PV findings into practical responses	Labeling modifications; changing the prescription status (over the counter or prescription only)
	Those who finance health services and medicines (such as insurance authorities)	Changing benefit packages, for instance, by excluding from public funding medicines with unfavorable risk-benefit ratios
	Training institutions to facilitate the adoption of new risk messages	This requires a closer relationship between PV activities and results to improve teaching and updates on the selection, prescription, and rational use of medicines.
	Quality assurance agencies to facilitate the enhancement of behavior change in issuing prescriptions	Promotion of local drug utilization studies (therapeutic audit studies), self-audit activities, and comparisons with peers)

3.3 Essential PV Pillars

There are three essential pillars or building blocks in the successful completion of core PV activities. Their realization will ensure the path toward the maturity of a national PV system.

- *First pillar: a statutory provision.* The first pillar is the existence of a statutory PV provision (national policy or legislation), a requirement to define PV activities, a model of the PV program, the deployment of PV, the budget allocated to the PV program to support administrative, research, and information activities as part of the national health care system, the definition of the relationship with manufacturers on safety issues, and international participation, including membership in the WHO Program for International Drug Monitoring (WHO PIDM) (Peters et al. 2021).[6]
- *Second pillar: a PV center.* The second pillar is a PV center run by well-trained health professionals who form a multidisciplinary team with clinic and pharmacy backgrounds, training in pharmacoepidemiology, and skills in research and communication with health professionals and the general public.
- *Third pillar: PV reporters and effective PV reporting systems.* Engaged reporters and good-quality reports constitute the third pillar. Underreporting is the Achilles heel of any national PV program based on spontaneous reporting. The reasons for underreporting have been largely explored, but not addressed satisfactorily (Edwards 2001). Even compulsory reporting by manufacturers is beset with problems, such as low-quality reporting (Plessis et al. 2017).

3.4 PV Methods

Table 2 summarizes the main characteristics of PV data collection methods. The most important, least expensive, simplest, and most widely used method of detecting potential ADRs over the last half century has been the spontaneous and voluntary reporting of cases by health care providers and patients, as well as by drug manufacturers, in accordance with mandatory regulatory requirements. A good example of this passive reporting system is the Yellow Card Scheme in the United Kingdom that is operated by the Medicines and Healthcare Products Regulatory Agency and the Commission on Human Medicines. The system is used to collect data on suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued by prescription or purchased over the counter (Coleman and Pontefract 2016).

The major limitations of the system of spontaneous ADR reporting are well known: the poor quality of the reports submitted; the significant underreporting; the difficulty in calculating rates because of incomplete numerator data, along with unreliable consumption denominators; and the constraints on the ability to establish cause and effect (Lexchin 2006).

Active surveillance involves methodically searching for ADRs at sentinel site facilities, in addition to following up with patients who have been exposed to medicines of interest (SPS 2009b). The design of this method facilitates the collection of more comprehensive ADR data relative to passive surveillance by helping obtain a denominator on the persons exposed to medications of interest. This allows for the calculation of ADR rates, which can highlight medication safety among vulnerable populations, such as women of childbearing age. Formal observational studies, such as case-control and cohort studies, identify and quantify the strength of associations between a given medication exposure and adverse health outcome (see Dellicour et al. 2007; Ward et al. 2007; WHO and MMV 2009). Pharmaceutical manufacturers sometimes conduct post authorization studies, which, among other aims, may help identify significant risks.

Several methods that have proven successful in stimulating ADR reporting among the medical community include educating doctors on the need to report; familiarizing doctors with the reporting system in general, along with the forms and guidelines; and providing doctors with follow-up on the reports they have filed (Goldman 2004).

[6] WHO PIDM (Programme for International Drug Monitoring), World Health Organization, Geneva, https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm.

Table 2 PV Methods, Strengths and Weaknesses

Type		Characteristics/Structure	Strengths	Weaknesses
Reactive	Passive	Spontaneous reporting by health care professionals received by the PV center. Compulsory reporting by manufacturers. Any adverse reaction. Any product. Adverse events do not necessarily indicate causality involving the suspected medicine. The adverse reaction had already happened.	Unspecific. Covers all medicines and their adverse effects. Covers the whole population. Inversed tree-like structure: from patients to the national PV program to the WHO PIDM. Can detect rare and very rare adverse events not identified in clinical trials. Online reporting can increase the reporting rate. Continuous in time.	Underreporting and poor information can be limiting aspects. Limited clinical and laboratory information. Requires an individual causality assessment. Some reports have poor information; this hinders the causality assessment.
	Active	The PV center or researchers design a specific study to stimulate or reveal adverse reactions. Usually covers a specific adverse reaction or a specific medicine or vaccine. Usually for serious adverse reactions or new medicines. Usually in controlled settings (for example, a hospital, an emergency unit, or specialized external consultation). The adverse reaction had already happened.	Designed to involve health professionals managing specific patients or medicines. Helps strengthen signals detected by passive reporting. Helps identify and define the characteristics of rare adverse reactions. Electronic records can help in the identification of cases. Short-time studies.	It cannot be maintained for a long time. It requires additional human resources for each intervention. It is useful only for selected products.
Proactive	Preventive	It involves all actions conducted to avoid or reduce the chance of developing an adverse reaction. It may cover specific and unspecific adverse reactions and medicines or vaccines. Examples: taking actions to increase patient safety and avoid medication errors; checking for potential drug-drug interactions before prescribing; avoiding the prescription of certain medicines for patients at risk; avoiding the prescription of low benefit–risk medicines; patient counseling in pharmacies to reduce self-medication. The adverse reaction has not happened yet.	Patients did not have the chance to develop adverse reactions. Increases the efficiency of treatments. Reduces some adverse reactions. Electronic prescription tools are useful. Once a specific decision tree or algorithm is established, it can be applied without additional effort.	Its benefits can only be quantified by indirect measures. It requires the development of a preventive culture. Some prescribers can feel that their decisions are monitored.

Computer technology, which allows multiple databases to be linked, is also helping in the investigation of drug safety issues. The widespread use of electronic medical record databases has enhanced patient safety through the automation of ADR signal detection, thereby improving health care service delivery. Additionally, new tools that aid decision-making in electronic prescriptions have demonstrated their value in preventing ADRs (Pons-Mesquida et al. 2021).

The digitalization of prescriptions and medical records has huge potential to transform PV, especially in prevention and reporting. This area is quite new, and only a few studies from the PV perspective have been conducted. In practice, this point of maturity has not yet been reached in many countries. Moreover, in some countries where investments have been made in these kinds of health technologies, practical problems have arisen, such as a lack of compatibility among systems and the inclusion of incomplete or inaccurate information in systems because of the human factor.

These electronic prescription tools are based on alerting the prescriber, the pharmacist, or the nurse about potential problems, such as medication errors, drug-drug interactions, duplicate treatments, or medicines inappropriate for certain patients. However, these are only alerts; health care professionals must actively acknowledge them and act. In practice, some of these alerts generate fatigue, and the professionals may not even read them. These types of tools have proven useful, but realizing their potential will require more development and dissemination.

3.5 Assessing PV Systems

The assessment of the status of PV systems and the diagnosis of system strengths, weaknesses, and gaps are carried out using a PV assessment methodology. The assessment covers all aspects of the PV system: people, functions, and structures. Various indicators are used to measure the existence and performance, as well as the achievements, growth, or lack of growth of PV systems. Two reports—*Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries* (SPS 2009a) and "WHO Pharmacovigilance Indicators: A Practical Manual for the Assessment of Pharmacovigilance Systems" (WHO 2015)—each include widely used and well-tested sets of indicators to measure the qualities of a system.

The results of these assessments also allow countries to benchmark and compare the performance of local PV systems with counterpart systems in other nations and enable the quantification of the impact of future policy and public health interventions to ensure the safety of pharmaceutical products on the market (Qato 2018).

Overall, the availability of these sets of PV indicators provides objective measures to describe the PV situation in a country (SPS 2009b). This helps accomplish the following:

- Assess PV activities in health care facilities and across regions and nationwide
- Assess the capacity of and for PV at these levels
- Provide tools for the supervision and monitoring of PV activities
- Gauge progress and enable the prioritization of efforts based on the assessment
- Enable the comparison of PV activities across health facilities and geographical regions at a given time and at different times
- Supply tools for measuring the impact of interventions
- Provide information to enable governments and other stakeholders to take appropriate action in ensuring drug safety
- Maintain confidence by properly responding to patients and to community concerns

4. The Development of National Pharmacovigilance Systems

4.1 The Thalidomide Tragedy and Its Impact on the Development of PV

PV was first implemented about 170 years ago, although it was not known as pharmacovigilance at the time (Fornasier et al. 2018). Its importance began to be realized as a result of deaths and alerts raised by clinicians and the public about the safety of anesthesia in England, which led the medical journal, *The Lancet*, to form a commission to investigate the issue. The results were published in *The Lancet* in 1893 (Lancet Commission on Anaesthetics 1893). The enactment of the US Federal Food and Drug Act on June 30, 1906, which prohibited the interstate transport of unlawful food and drugs under penalty of seizure of the questionable products and prosecution of the responsible parties, added momentum at the international level to the development of PV as a structured health activity to safeguard people's safety (FDA 2019). The basis of the law, however, resided in the regulation of product labeling rather than the premarket assessment and approval of products.

If one case was the real game changer in drug safety monitoring, it was undoubtfully the well-known tragedy of thousands of babies with phocomelia, a condition that involves malformations of human arms and legs. The babies had been born to mothers exposed to thalidomide, a sedative marketed in 1957 that was later found to be effective at treating morning sickness. It was believed to be so safe that it was available over the counter in several countries. However, it was withdrawn from most of the pharmaceutical markets after the appearance of these congenital malformations between 1959 and 1962.

The thalidomide tragedy raised concerns about the safety of medicines and the potential dangers to public health associated with unexpected adverse reactions to medicines. It highlighted the need for better safety and efficacy studies before market authorization of a new medicine, including the repurposed use of an existing medicine. It also raised concerns about the gaps in safety knowledge before a drug has been used in large populations and the need for accurate postmarket safety monitoring for the timely detection of any previously unknown ADRs, serious reactions, or unexpected clusters of side effects.

The short-term response in this context was the adoption of resolution WHA 16.36 during the 16th World Health Assembly in 1963, reaffirming the need for early action to promote the rapid dissemination of information on ADRs. This led to the creation of a WHO pilot research project with the participation of nine countries to develop a system that could be implemented internationally for the detection of previously unknown or poorly understood adverse effects of medicines. The initial activities of the pilot project culminated in the establishment of the WHO PIDM, which is discussed below.

4.2 Achievements

The WHO PIDM has grown to become a global network of national PV centers coordinated by the Uppsala Monitoring Center (UMC).[7] To improve patient therapy and public health worldwide, the UMC collects, assesses, and communicates information from national PV programs on the harm, effectiveness, and risks of drugs and other substances

[7] "The WHO Programme for International Drug Monitoring (PIDM) and How to Join," World Health Organization, Geneva, https://whopvresources.org/who_pidm.php.

used in medicine. The center also collaborates with countries in the development and practice of PV.

After the launch of the PIDM by nine pioneer countries in 1968, there was a wave of early adopters (21 countries by 1985), followed by an early majority (104 countries by 2010) and a late majority (155 countries by March 2023). At the WHO PIDM annual meeting that was held in Rabat, Morocco, in March 2023, the network included 155 full member countries and 22 associate members working together to monitor the safety of medicines and vaccines based on the spontaneous reporting of suspected ADRs under shared rules and a single database. The WHO PIDM had thus become a global, comprehensive network involving health professionals, patients, and manufacturers (Wang, Figueras, et al. 2023c).

The growth over the past 55 years has paralleled significant progress in pharmacotherapy during the golden age of chemical medicines or small molecules. Later, there was the dawn and expansion of biological drugs, the consolidation of evidence-based medicine, the advances in ethics applied to medicine research, the increasing access to information and electronic databases, and the appearance of artificial intelligence as a tool to help in the early detection of signals and relevant clusters.

The most comprehensive assessment of the performance of national PV systems is a classical survey conducted by Sten Olsson and his UMC team (Olsson et al. 2010). Although the landscape has changed significantly over the last decade, examining the study's results is still useful. According to Olsson and colleagues, almost half the PV centers were established during the 1990s, and the other half was set up later. These PV centers were affiliated with drug regulatory agencies (69 percent), ministries of health (20 percent), or universities or scientific bodies (9 percent) in a high proportion of countries (n = 42). Many PV centers were also involved in other activities, such as providing drug information (63 percent), promoting patient safety (52 percent), fostering the rational use of drugs (46 percent), or disseminating information on poisons (15 percent). In addition, seven countries had sentinel sites to monitor HIV/AIDS patients and other special groups. Few countries (23 of 55) had any budget allocated for PV. Activities were sponsored by public health programs (44 percent), the Global Fund to Fight AIDS, Tuberculosis, and Malaria (36 percent), universities (26 percent), poison centers (21 percent), the global nonprofit Management Sciences for Health (18 percent), or the International Network for Rational Use of Drugs (15 percent).

The commitments of countries and the technical support of the UMC, other agencies, and funding stakeholders have contributed to the development and strengthening of national PV systems. The support provided by regional organizations has also been important for harmonization in data collection, the training of personnel, and the undertaking of regional analysis of specific safety signals. This is the case of the European Union (EU) under the lead of the European Medicines Agency (EMA) or the common PV approach adopted for small island countries in the Caribbean region coordinated by the Caribbean Public Health Agency (CARPHA).

4.3 Challenges

Low- and middle-income countries face unique challenges in establishing functional PV systems. The challenges include difficulties in conceptualizing the idea of a comprehensive PV system; making the necessary legislative changes to allow establishment, recognition, and operation; allocating well-trained health professionals to run the system and engage sufficient PV reporters to be able to monitor ADEs in a country; interacting with the WHO PIDM network and other peer organizations at the international level; and obtaining regular funding for administrative, research, and dissemination activities.

Although national regulatory authorities have legal provisions on PV and postmarket surveillance at their disposal, as in the case of countries in the Americas, no clear approaches are being implemented to support the performance of the required regulatory activities, and resources are often shifted rather randomly among government entities (PAHO 2022).

A challenge that merits attention is the development of PV as an integral element of the health system and the continuous enhancement of the capacity

to monitor and assess the growing number and complexity of new drugs entering the market, in addition to the pharmaceutical products already being prescribed and used. For example, a study in Africa indicates that PV activities are hindered by the scarcity of well-trained personnel, the lack of budgetary support by governments, high turnover among PV staff, whose training involves substantial resources, and the lack of awareness about PV among health care workers, decision-makers, and consumers (Kiguba, Olsson, and Waitt 2023).

PV systems are heavily reliant on voluntary reporting. Partly caused by the spontaneous method used by PV centers to collect information, underreporting is a common problem in countries. Some staff do not report ADRs because they may not be aware of the reporting procedure, do not have the time or forget, are fearful of litigation or have doubts about the diagnoses, or simply misdiagnose the event. Staff training in PV centers therefore persists as an ongoing challenge in the effort to ensure that all ADRs are adequately reported and resolved. Low spontaneous reporting rates and the poor quality of reports also hinder robust signal detection analyses.

Another challenge concerns the need to strengthen coordination and collaboration with other programs and institutions, particularly between public health programs and national medicines regulatory authorities, to enable the active engagement and support of all stakeholders in PV activities. This is needed to ensure that PV information is translated into assessments that inform and guide policy makers, program managers, and service providers, help communicate drug safety concerns clearly to the general public, and, where appropriate, contribute to regulatory action.

4.4 The Lessons of Successful PV Programs

While there are accepted principles, functions, and minimum standards at the international level for a functional PV system, there is no universal all-fit method for developing a national or regional PV system. The adoption and adaptation of the principles, functions, and minimum standards are influenced by contextual factors, such as organizational arrangement, development priorities, policies, legal and regulatory structures, institutional capacity, and the available resources that are unique to each country or region.

Over the past six decades, some countries and regions reviewed for this work, such as Brazil, Ghana, Korea, Spain, the Caribbean Community, and the EU, have been successful in developing robust national and regional PV systems that are well structured and rely on standardized data collection tools. Table 3 summarizes some of the characteristics of these PV systems.

Table 3 The Development of PV Systems, Selected Countries and Regions

Country, region (starting year)	Characteristics, structure	Specific game changers, strategies
National approach to pharmacovigilance		
Brazil (2001)	Decentralized: 27 state centers coordinated by the Brazilian Health Surveillance Agency (ANVISA) Funding: each state government, as part of the local center of health surveillance	• A number of uncoordinated PV activities in various university departments and among patient advocacy groups before the establishment of a federal agency to coordinate the initiatives. Early PV activities were carried out in certain states (for example, Ceará, Rio de Janeiro, São Paulo). • Once ANVISA launched national activities, individual programs were integrated into a harmonized PV system covering 26 states, using a common reporting form and, since 2018, a common database (VigiMed). The consolidation of this effort in the states proceeded, however, at a varying pace that was determined by the availability of resources and trained health professionals. • A shared objective and dedicated human resources were crucial in the initial stage, given the size and the heterogeneity of the country.
Ghana (2001)	The country is among the pioneers of PV in the Africa region. The National Pharmacovigilance Center was established in 2001 under the Food and Drugs Authority and was accepted into the WHO PIDM. Since 2012, Ghana's PV activity is coordinated by the Safety Monitoring and Clinical Trials Division of the authority.	• Involving vertical public health programs that monitor the safety of the medicines administered represented a quick way to start receiving reports and consolidating PV activities, but also to increase the effectiveness of these programs by understanding the adverse effects of the medicines used and increase patient adherence. The latter helps reduce drug resistance to medicines administered in tuberculosis, malaria, and HIV/AIDS programs. • Legislation exists to support PV activities; decentralized regionally to ensure nationwide coverage. • Use of institutional contact persons in health care facilities as PV liaison persons.
Korea, Rep. of (1992)	Decentralized system with a shared database and coordinated by the Korea Institute of Drug Safety and Risk Management (KIDS).	• Early creation of the KIDS: investing in strengthening one national institution that covers various aspects of the use of medicines (PV, drug utilization, drug selection, risk management, and information) is a viable way to ensure patient safety, promote high-quality research, and become a model in the region. • Built up following a systemic approach (legislation + institutional base + training) and taking advantage of new technologies (reporting system).
Spain (1984)	Decentralized: 17 regional centers coordinated by the Spanish Medicines Agency. Funding: under each local government	• PV activities were undertaken within a small, but well-considered academic institution in Catalonia. In parallel, the center included clinical pharmacology in medical training, in addition to editing a pocket-size medicine formulary and a monthly safety bulletin. The PV effort was scaled up and evolved into a national program with the support of appropriate legislation, resources, and training.

Table 3 *Continued*

Regional approach		
Caribbean Public Health Agency (CARPHA 2017)	CARPHA provides a subregional mechanism that supports regulatory action to ensure access to safe medicines (*VigiCarib*).	• The 15 Caribbean Community countries are mainly small island countries. *VigiCarib* offers countries that have few available human resources the possibility to participate in a regional PV approach, although governments can report directly to the WHO PIDM if they wish and have the capacity. • Focal points collect local reports, maintain local databases, and submit reports to *VigiCarib*. Technical officers receive, review, and follow up on reports, conduct searches for safety information on medicines and vaccines, and prepare aggregate reports. • A program manager runs *VigiCarib* network operations, identifies and communicates decision-making issues, reviews data and operational procedures, develops recommendations, and supports focal points. • Shares information on suspected ADRs and quality issues for member states to monitor locally
European Medicines Agency (EMA 2012)	Decentralized. Each member state has its own PV program. Coordination: EMA. Each member state funds its national PV program. EMA can fund specific projects.	• The framework of the EU favors harmonization in various initiatives among member states, including medicines approvals and safety monitoring and evaluation. • Various committees are involve, as follows: ° The Committee for Medicinal Products for Human Use (CHMP) is responsible for human medicines ° The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for assessing and monitoring the safety of medicines • Each country provides experts for the committees. EMA provides support in harmonization and training.

4.5 Key Lessons

The following experiences offer valuable lessons to other countries or regions in the development of key aspects of functional PV systems.

1. *Legal and institutional aspects.* The experiences of Korea and the EU demonstrate that building the capacity for a comprehensive PV system in a country or region involves the development of a robust legislative framework, a functional and sustainable regulatory and organizational structure, and guidelines for PV and medicine safety monitoring.

   In the case of Korea, the national PV system has been the result of a continuous and sustained government effort, from small pilot projects to a nationwide monitoring network, over the past three decades (Wang, Marquez, et al. 2023a). The Pharmaceutical Affairs Act, adopted in 1960 and amended over the years, regulates the manufacture, import, sale, and advertising of drug products, sets the conditions for licensing, establishing, and operating pharmacies, and governs the operation of the PV system. The Korea Institute of Drug Safety and Risk Management (KIDS), established in 2012 under the act, operates as a dedicated agency of the Ministry of Food and Drug Safety and supports evidence-based decisions on drug safety.

   At a regional level, the European drug regulatory system is based on a network of around 50 regulatory authorities in the 30 European Economic Area countries, including the European Commission and the EMA (Wang, Figueras, et al. 2023b). Established in 1995, the EMA operates at the heart of the network, coordinating and supporting interactions among more than 50 national competent authorities in human and veterinary medicine and playing

a major role in the harmonization of European and international drug regulations.

2. *Levering disease-specific public health programs.* Several countries have public health programs that are disease-specific and often operate separately from the rest of the health system. These programs, which are funded with the support of external donor organizations, operate vertical treatment initiatives that depend on good PV practices to monitor and assess ADRs, particularly if treatment is being scaled up, such as antiretroviral treatment for HIV/AIDS, or if the standard treatment guidelines change, such as the switch to artemisinin-based combination therapy for the treatment of nonsevere malaria caused by *Plasmodium vivax*. This is also the case of immunization programs, particularly if new vaccines are introduced, for instance, for COVID-19. In some countries, the PV arrangements established under these public health programs provide a model for the eventual establishment of a national PV system.

   In Ghana, for example, the routine reporting of adverse events following immunization (AEFI) began with the launch of the Expanded Program on Immunization in 1978 and, later, was continued by the Food and Drugs Authority beginning in 2001 upon establishment of the National Pharmacovigilance Center. The surveillance system was created with the overall aim of promptly detecting and managing AEFI, real or perceived, and contributing to the credibility of immunization programs by preventing inappropriate responses to reports of AEFI that could lead to crises or vaccine-hesitancy among the population in the absence of a surveillance system (Laryea et al. 2022).

3. *The active engagement and participation of various stakeholders.* Functional, well-structured PV systems result from collaborative efforts among various stakeholders. Clearly defined roles and responsibilities among expert advisory committees, public health programs, hospitals and clinics, health care providers, professional associations, academic institutions, pharmaceutical manufacturers, importers, wholesalers and retailers, consumers, and media are critical for the development of PV systems.

   The important role that stakeholders may play in the development of a comprehensive PV system is illustrated by the experience in Spain. The Catalan Institute of Pharmacology, as part of the Autonomous University of Barcelona and the associated teaching hospital, coordinated activities related to the safe use of medicines in the early 1980s, a moment in which the concern about the safety of medicines was low in the country (Wang, Figueras, et al. 2023d). In addition to pilot PV activities in the region, the first pocket-size therapeutic formulary book was published, and a quarterly four-page bulletin was freely distributed to all practitioners as a way to spread the seed of concern about medicines safety and the need for surveillance. This subnational academic initiative laid the groundwork for the development of the national PV system, which consists of a national PV coordinating center in the Spanish Medicines Agency and 17 regional centers located across the country. The experience shows that involving university groups as part of a PV system helps lever existing research capacity for data analysis and the formulation of clinical guidelines and protocols.

   Likewise, in Ghana, the operation of the AEFI surveillance system is a collaborative effort between the Expanded Program on Immunization of the Ghana Health Service and the Food and Drugs Authority that involves the collection and collation of routine data using the health structures of the Ghana Health Service (Laryea et al. 2022). Case reporting is passive, that is, caregivers and vaccinees report adverse events to health facilities, and the health facilities record reported events using a standard case reporting form to submit the report to the district health directorate, where the data forms are entered into the District Health Information Management System II and transmitted to the national level through an intervening regional focal point. Data are aggregated at the regional and national levels. Some notifications are sent directly from the community or the health facility to the Food and Drugs Authority through an electronic reporting system.

4. *Resource allocation to support the operation of the PV system.* Assuring that infrastructure and staffing needs are filled and supported by predictable and sustained budgetary allocations is a critical input for a functional PV system. In particular, continuous financial support for PV activities is essential to ensuring that well-trained health professionals remain in the system and stay motivated to improve their knowledge, enabling the system to evolve from a simple administrative committee into a functional reference center for the continuous monitoring of medicines safety.

   In Korea, KIDS operates under funding from the Ministry of Food and Drug Safety, which provides about 68 percent of the total KID revenue (Wang, Marquez, et al. 2023a). Additional funding comes from contracting out research, evaluation, and services ordered by other government entities.

   In decentralized national health systems, such as in Spain, each regional PV center depends on the annual budget defined by regional health authorities (Wang, Figueras, et al. 2023d). In some cases, the PV centers are integrated into the health department or into a public hospital; in other cases, the PV centers are run by university researchers and professors.

   In the case of EMA, approximately 86 percent of its budget (€357.7 million in 2022) is expected to come from fees for processing applications from companies that want to introduce a medicine on the EU market (Wang, Figueras, et al. 2023b). EMA also charges fees for services related to marketing medicines in the EU in areas such as scientific advice, inspections, and the establishment of maximum residue limits. The remaining 14 percent (€55.2 million in 2022) is expected from the EU contribution for public health issues, which mainly supports policies for orphan and pediatric medicines, advanced therapies, and micro, small, and medium enterprises. Some of these revenues are redistributed to EU member countries because EMA coordinates the scientific evaluation of applications and related work with the national medicines regulatory authorities in EU members. As part of this arrangement, EMA compensates the national authorities for their related work and the involvement of their staff members in EMA scientific committees, working groups, and other activities. The national PV systems receive direct funding from their governments.

   Half the funding of CARPHA is provided by member states, and the other half by international partners (Wang, Figueras, Extavour, et al. 2023). CARPHA offers a good practical example of South-South-North cooperation as Canada, France, Germany, the Netherlands, the United Kingdom, the United States, the EU, and Latin American countries share intertwined interests in the Caribbean region (Hospedales 2019).

5. *Capacity development.* Increased awareness among health care professionals of the importance of ADRs and of the development of skills and competencies among PV personnel (for instance, surveillance methods) is crucial for the operation of an effective PV system.

   In Korea, for instance, KIDS exercises a critical function in education and promotion on PV and drug safety (Wang, Marquez, et al. 2023a). KIDS provides education on PV and drug safety among the public and among health care professionals and relevant organizations. The KIDS regional PV centers conduct related activities periodically, including the production and distribution of newsletters, press releases, and bulletin updates.

6. *Drug safety monitoring, policy making, and regulatory action.* Pivotal functions of a PV system are the monitoring, detection, reporting, evaluation, and documentation of drug safety data as well as intervening, gathering information from, and providing educational feedback to prescribers, health care workers, other health care professionals, and consumers.

   The Korean PV system offers a good example of how these functions are structured and operate in practice (Wang, Marquez, et al. 2023a). KIDS fosters voluntary ADR reporting by health care providers, patients, and pharmaceutical companies, assesses drug safety information, performs causality assessments, develops drug utilization review criteria, disseminates drug safety information, and provides education to the general public. The Korean Adverse Event Reporting System, a computerized

ADE reporting system developed by KIDS in 2012, contains more than 1 million ADE reports from the various PV reporters, as well as reports based on post marketing surveillance; observational studies, such as pharmacoepidemiologic studies, to collect safety information on drug products; and reports from other drug adverse reaction surveillance programs. If new ADEs are detected after drug approval, the Ministry of Food and Drug Safety takes action on the basis of guidance by KIDS to inform the public, change a drug's label, or remove a product from the market.

The experience of the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária, ANVISA*), a regulatory body of the Brazilian government that is independent of the Ministry of Health and that was established by Law 9782 of 1999, offers another good example (Wang, Figueras, et al. 2023a). *ANVISA* deals with various aspects of health monitoring, including the authorization and safety of medicines. This has allowed the linking of PV with other monitoring programs, such as hemovigilance and the surveillance of medical supplies. To facilitate ADE reporting, *ANVISA* has provided all health professionals with access to the National System for Health Monitoring Reporting (Sistema Nacional de Notificações para a Vigilância Sanitária), a national web-based computerized reporting system launched in 2006 to receive, register, and process reports of suspected and confirmed cases of ADEs and technical complaints, including reports of suspected ADRs, cases of therapeutic inefficacy, and medication errors causing ADRs. ANVISA has also had a leading role in establishing a sentinel network (*rede sentinela*) involving hundreds of hospitals across all the states of Brazil. The sentinel network includes the participation of health care professionals dedicated to monitoring the safety of medicines and other medical technologies. The state PV programs are being consolidated under the umbrella of the network, which thus acts as a permanent observatory of various aspects of the safety of medicines and health technologies. The network has thereby helped strengthen the knowledge of health professionals about safety monitoring activities.

Benefits of regional PV arrangements. The requirements behind the demand to institute and maintain a functioning PV system may be difficult to meet in countries that have institutional limitations and resource constraints. This is the case of the small countries and territories of the Caribbean Community. These economies have limited capacity and face constraints in implementing core drug regulatory functions to ensure access to safe medicines, including marketing authorization, PV and post marketing surveillance, legislation, and resources. CARPHA provides a dedicated subregional mechanism, the Caribbean Regulatory System, to support pharmaceutical regulation. The system plays a critical role in helping overcome individual country and territory limitations and constraints in ensuring access to safe medicines among Caribbean Community member states (Wang, Figueras, Extavour, et al. 2023). It includes a subregional system for reporting ADEs and substandard and falsified products (*VigiCarib*) and a regional post marketing drug quality testing program through its Medicines Quality Control and Surveillance Department. CARPHA is a good example of a subregional approach to facilitating well-functioning post marketing monitoring activities, including PV. CARPHA is well established, integrates lessons from more experienced regulatory authorities, and supports small countries and territories without specific PV programs, thus helping ensure the safety, quality, and effectiveness of the medicines and vaccines used in the region. A key lesson of the experience of CARPHA is that regional initiatives and arrangements are complex and require clear objectives, harmonization, respect for individual member countries and territories, and mutual trust. They also require the development of policies, procedures, communication mechanisms, staffing arrangements, and engagement with member states, other partners, and industry.

In contrast, in a region with consolidated national PV systems, such as among EU countries, the region as a whole may benefit from an expanded centralized data and information repository. The repository may be used to consolidate and assess the report submissions of individual countries following a harmonized approach, such as the one adopted among the EU member states and EMA in interpreting and

applying European Commission directives on the demonstration of quality, safety, and efficacy. The individual countries also benefit from participation in the regional PV system. For example, the system facilitates access to reports from a range of countries on potential safety signals related to the use of new medications, and PV specialists in all member countries are enabled to further their professional development by taking part in the work of the EMA scientific committees. EMA may also assist a country in reaching policy decisions if the country does not have a strong PV capacity, and EMA may likewise serve as an impartial referee in cases of a safety concern involving local manufacturers.

5. The Contribution of PV to Building Health System Resilience

In a health system, resilience is the ability to prepare for, manage (absorb, adapt, and transform), and learn from shocks (Sagan et al. 2022). These shocks are not predictable and enduring stresses, but sudden and extreme changes, such as a pandemic, that affect a health system. Medicines, vaccines, and other therapies are critical countermeasures both during normal times and in a public health crisis. Although indispensable for improving health outcomes, medicines, vaccines, and their administration and use may produce adverse effects.

In post marketing medicine surveillance, PV is crucial to quantifying previously recognized adverse events and identifying previously unrecognized adverse events to evaluate the effectiveness of medicines in real-world situations and, thanks to this knowledge, decrease the mortality and morbidity risks associated with ADEs. Building PV capacity should thus be understood as a critical public good investment by governments seeking to build resilience in a health system (Chandler et al. 2020).

PV can provide support for the performance of various functions in a health system, such as collecting and assessing data on prescribed and dispensed medicines, as well as on the utilization of health services and the outcomes of treatment (Wang, Marquez, et al. 2023b) (table 4). Hence, a health system that includes PV can promote the safety of medications by minimizing the occurrence of ADRs; informing health care providers, regulators, manufacturers, and consumers to take remedial actions and adopt preventive measures to avoid ADRs in future patients; and improving how medicines are prescribed and used (FIP 2006). Risk reduction actions may be (a) regulatory, such as withdrawing marketing authorization or recalling a medication; (b) managerial, such as modifying coverage conditions in drug benefit plans or modifying prices as in countries of the Organization for Economic Co-operation and Development (OECD 2019), revising formularies in health facilities, or instituting drug distribution controls; or (c) educational, such as teaching prescribers about medicine-medicine interactions or proper product handling, thereby improving communication with patients and the general public on the evidence derived from routinely collected data to confirm or counter suspected safety concerns.

Table 4 Areas of PV Intervention and Contribution in Health Systems

Area of intervention	PV action and result
Drug policy and regulation	The provision of good-quality, safe, and effective medicines and their appropriate use are the responsibility of national governments. PV contributes to the assessment of the value of the medicines in use in health care systems and, by helping ensure that risks in medicine use are anticipated and managed, provides information to policy makers and regulators on the amendment of recommendations on the use of the medicines and the adoption of regulatory action, as well as to program managers to inform decisions on the coverage conditions or prices for medicines.
Medical care services	Monitoring the use of medicines in routine clinical practice helps identify the emergence of unanticipated outcomes (rare or delayed adverse effects not detectable in clinical trials; variable clinical results) and reveals gaps between efficacy (benefits assessed in clinical trials) and effectiveness (benefits observed in clinical practice). The timely review of incoming data and real-time signal detection can provide important safety information and guide the work of health care providers, protecting the population from ADRs and ensuring that the use of pharmaceutical products contributes to good health outcomes. Evidence from routinely collected data is used to drive changes in clinical guidelines and care protocols. PV has the potential to strengthen current antimicrobial stewardship strategies because PV data can help identify antimicrobial resistance and prevent the inappropriate use of antibiotics (Habarugira, Härmark, and Figueras 2021).
Public health programs	Medicine safety monitoring is crucial to public health programs for disease control at the population level. For example, many tuberculosis programs have introduced and institutionalized active drug safety monitoring and management platforms for drug-resistant tuberculosis; the introduction of novel medicines and regimens for antiretroviral treatment for HIV/AIDS has also required comprehensive surveillance systems for ADRs; PV has been of great importance in malaria control programs given the increasing resistance to existing antimalarial medicines that has led countries to switch to combinations of various artemisinin derivatives as their first- and second-line treatments for malaria.
Eco-pharmacovigilance	Surveillance of the effects of drug residues in the environment, such as antibiotics, psychoactive drugs, and hormones, on human health and livestock. Biologically active compounds are specially designed to be effective even at low concentration levels. Pharmaceuticals in the environment may thus have adverse impacts on the health of human beings or other nontargeted organisms after long-term exposure (Wang et al. 2018).
Strategic communication	By providing evidence derived from routinely collected data to confirm or counter suspected medicine safety concerns, PV improves communication between health professionals with patients and the general public and educates health professionals in understanding the effectiveness or risk of medicines that they prescribe. The effective communication of the risks to the safety of drugs is a vital task to be carried out by governments and health care providers, as well as the pharmaceutical industry, to address the public perception of the hazards associated with medicines and build trust in the health system and other government actions.
Adverse drug reaction relief programs	Manufacturing, selling, prescribing, or dispensing medicines may have serious consequences that are the object of liability trial. PV can inform such trials and aid therapeutic decisions or causality analyses associated with adverse events, including medical and other scientific evidence of reported outcomes (Edwards and Body 2012). Some ADR relief services require criteria for compensation eligibility, including the proper use of the medication associated with the adverse event and any reasonably plausible association between the drug and the adverse event (Watanabe et al. 2019). Based on the results of causality assessments in ADRs, governments may offer compensation for victims who die, are injured, or are hospitalized because of unexpected ADRs despite proper care, using relief systems operated with financial assistance from pharmaceutical companies. For instance, see Adverse Drug Case (dashboard), Korea Institute of Drug Safety and Risk Management, Anyang, Gyeonggi, Republic of Korea, https://www.drugsafe.or.kr/iwt/ds/ko/report/WhatIsADR.do.

6. Policy Considerations

The previous sections summarize the information available in scientific journals and reports and in country and regional case studies. This fact must be highlighted because no experimental study has been conducted so far comparing the efficiency and effectiveness of various approaches to establishing and developing a PV system. Nonetheless, the documented performance and results achieved through the PV systems in operation in more than 150 countries have allowed us to formulate some policy considerations for governments and other national stakeholders, as well as for developments partners. These are presented below.

6.1 Considerations for Governments and National Stakeholders

The key to ensuring the development of comprehensive PV systems involves highlighting the importance of the systems and their sometimes overlooked or poorly explored role beyond collecting reports, uploading the reports to a PV database, and preparing an annual activity summary. PV is an essential public health function in a health system to help secure the safe and effective use of medicines.

Strategic planning and phased build-up. Accumulated international experience suggests that countries can create such systems through careful strategic planning and a phased build-up. This requires political commitment, coupled with dedicated technical and financial support, to establish and sustain robust medium- and long-term legal structures and institutional arrangements. Given the public goods nature of PV, governments should take responsibility for financing PV activities.

Broad stakeholder participation. With the support of international partners, governments should also take charge of the mobilization and active involvement of various stakeholders in reviewing existing PV activities, identifying priorities for scaling-up efforts through a systems approach, and developing consensus on the role stakeholders might play in implementing a fully functioning PV system.

Active data collection. While spontaneous or passive approaches to data collection on and the assessment of ADEs have been the most common in various countries globally, governments should consider adopting active surveillance methods, including the use of registries, sentinel sites, and follow-up among patient cohorts, to overcome the underreporting and low-quality information associated with passive methods. This effort should also encompass attention to developments in information technology and advanced methodologies, including machine learning techniques and the availability of large amounts of electronic health care data, that offer the opportunity to leapfrog to the expansion of the PV capacity to optimize drug benefit-risk profile evaluations in real-world settings (Trifirò and Crisafulli 2022). Systematic clinical data mining may accelerate the speed at which ADE signals can be detected, thereby contributing to building health system resilience. Such an active drug safety surveillance system would allow drugs to be monitored longitudinally over their entire life cycle, providing regulatory authorities with timely access to new information with which to evaluate a drug's risk profile and minimize the safety concerns associated with the increased volume and complexity of new drugs and therapeutics regularly becoming available on the market.

Strategic communication. The effective communication of the risks to the safety of drugs is a vital task that needs to be carried out by governments and health care providers, as well as the pharmaceutical industry, to address the public perception of the hazards associated with medicines and build trust in the health system and other government

actions. Effective communication practices, the positive framing of mild side effects, and addressing misinformation related to vaccine adverse effects can reduce the concerns about these adverse effects (Motta et al. 2021; Rief 2021). Failure to communicate effectively to health care professionals and the public can lead to a loss of trust, the diminished reputation of regulators and other stakeholders, and the loss of lives (WHO 2020).

6.2 Considerations for Development Partners

Support for system development. International experience suggests that building a functioning and effective PV system that is sustainable requires a phased implementation process. This approach is needed to deal with capacity and financial constraints in low- and middle-income countries. The sustained technical and financial assistance of development partners is of paramount importance in complementing and supporting country efforts.

Technical assistance in specific areas. Based on their areas of interest and comparative advantages, development partners may choose to support specific PV activities, such as product quality monitoring; monitoring and reporting substandard and falsified products; the development of capacity in country organizations, such as national PV monitoring centers; or a focus on a particular disease, program, or group of pharmaceuticals, such as antiretrovirals, as the cornerstone for the development of comprehensive PV programs in a health system. Within health sector projects funded by international organizations, such as the World Bank, regional development banks, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, or bilateral organizations, support could be included for developing and strengthening key components of the PV system.

Promotion of stakeholder involvement. A critical area that may benefit from the technical assistance of development partners, such as the WHO, is the provision of assistance to countries in mapping all stakeholder roles and responsibilities in the system and in bringing stakeholders together to address PV as a common issue (SPS 2009b). The development of a shared framework for establishing or strengthening a PV system can also facilitate coordination among stakeholders. As part of a collaborative effort, partners can identify gaps and areas of duplication, as well as successes and strengths to build on and opportunities for streamlining and harmonizing roles and responsibilities.

A learning exchange among countries. Another area that merits support by international partners is the use of existing learning platforms or the development of new ones to foster the regular exchange of experiences, knowledge, and skills among countries, thereby promoting more well harmonized PV approaches.

Overall, in supporting future endeavors to strengthen PV capacity as part of building resilient health systems, international partners will be helping countries realize a basic tenet associated with the millennia-old Hippocratic oath, “First, do no harm,” which is at the core of public health and medical practice, the monitoring of the risk-benefit ratio of medicines, and efforts to improve patient safety and the quality of life.

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