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Do No Harm Situation Analysis

Safety Monitoring of Medicines and Vaccines

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Safety Monitoring of Medicines and Vaccines

A Situation Analysis

Table of Contents

Boxes

Figures

Tables

Reports in the *Pharmacovigilance* and *Essential Public Health Services* Series

Global

Synthesis Report on Pharmacovigilance: Why is the Safety of Medicines Important for Resilient Health Systems?

Positioning Report on Pharmacovigilance: The Value of Pharmacovigilance in Building Resilient Health Systems Post-COVID

Pharmacovigilance Situation Analysis Report: Safety Monitoring of Medicines and Vaccines

Regional

Realizing a Regional Approach to Pharmacovigilance: A Review of the European Union Approach

The Caribbean Regulatory System: A Subregional Approach for Efficient Medicine Registration and Vigilance

Financing of Essential Public Health Services in the Caribbean Region

Country Scope

Learning from the Republic of Korea: Building Health System Resilience

Learning from Best Practices: An Overview of the Republic of Korea Pharmacovigilance System

Pharmacovigilance in Brazil: Creating an Effective System in a Diverse Country

Starting and Strengthening a National Pharmacovigilance System: The Case of Catalan Regional Activities that Propelled the Spanish Pharmacovigilance System

Ghana's Pharmacovigilance Experience: From Vertical Program Activity to Nationwide System

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Acronyms

ADR	adverse drug reaction
AMRH	African Medicines Regulatory Harmonization
ASEAN	Association of Southeast Asian Nations
PANDRH	Pan American Network for Drug Regulatory Harmonization
NRA	national regulatory agency
NRAr	national regulatory authority of regional reference
PIDM	Program for International Drug Monitoring
PV	pharmacovigilance
UMC	Uppsala Monitoring Center
WHO	World Health Organization

Abstract

Medicines, vaccines, medical devices, and blood are commonly used to treat disease. Medicines deserve a special focus because almost any medical visit ends with at least one prescription. So, monitoring the safety and effectiveness of therapeutic treatments and procedures is crucial at both the individual and community levels. In the case of medicines and vaccines, this surveillance activity is known as pharmacovigilance.

Various methods are used to monitor the adverse and unwanted effects of medicinal products after they have received authorization for marketing, but reporting adverse reactions is the most widespread.

The network of the Program for International Drug Monitoring (PIDM), which is supported by the World Health Organization (WHO), involves more than 170 countries. Its activities were initiated in 1968. The WHO-PIDM is the world's most comprehensive network involving health professionals, patients, and manufacturers.

This situation analysis describes relevant aspects of the PIDM, including achievements and weak points. The analysis is the product of a systematic revision of studies that focus on the WHO-PIDM activities and related findings published in different medical journals and listed in PubMed.

Available information was selected and organized according to different topics and summarized and presented in the different sections of the report. As information for some countries and regions is lacking in the available literature, the report is not a comprehensive review of the pharmacovigilance across countries. The report, therefore, shows what is in place and highlight some of the difficulties faced by many countries, particularly low-and-middle income countries . It offers an overview of the (1) common points and failures; (2) the advantages of a national PV system; (3) the difficulties in scaling up and consolidating these systems; and (4) the advantages of regional collaboration.

This report is part of a series of companion reports on pharmacovigilance, that provide a detailed overview and discussion on technical aspects and country and regional experiences.

Involving more than 170 countries, The Program for International Drug Monitoring is the **most comprehensive** network of health professionals, patients, and health product manufacturers in the world.

Introduction

The aim of this Situation Analysis of Pharmacovigilance (PV) and PV activities is to review the existing literature that describe how the WHO PIDM has been developed, as well as achievements and difficulties experienced by some of the 170 countries that are part of that network.

To our knowledge, no previously published report describes the practical aspects of implementing PV systems at the national level and the difficulties faced in establishing them from a global perspective. The most comprehensive analysis was published in 2010 and included information from 55 countries.

The Analysis is the result of a review of the publications containing keywords such as “pharmacovigilance”, “surveillance”, “monitoring”, and/or “medicines” included in PubMed until March 2023. Additionally, this information has been complemented by reports and articles published by the Uppsala Monitoring Centre (UMC), that coordinates the WHO-PIDM. Hence, this report is a product of a revision of previously published papers and does not include primary data collected for its preparation.

The review is structured into two parts and populated them with specific experiences reported by the countries.

The first part describes the WHO-PIDM network; how was it created; the coordinating role of the UMC, and the evolution of the PV program that cover 170 countries; how national PV systems are evaluated; and the importance of VigiBase, the global PV database which facilitates the identification of harms of medicines and vaccines.

The second part describes the difficulties and results of PV from the national and regional perspectives, focusing on (but not limiting to) low-and middle-income economies. PV activities in high-income countries, such as the European Union countries, are the object of a separate case study.

This report is part of a series of companion reports on pharmacovigilance, that together provide a detailed overview and discussion on technical aspects and country and regional experiences.

1. The PIDM: A Global System

Thalidomide was the cause of an epidemic that affected at least 10,000 children and possibly as many as 100,000 children worldwide. The children were born with limb deformities to mothers who had used the medicine to relieve morning sickness during pregnancy (Vargesson and Stephens 2021). This was not the first disaster associated with drugs. Still, because of the relevance of the congenital malformations, the number of victims, and the worldwide impact, this episode prompted a global response to minimize the chances of similar disasters in the future. One of these responses was the adoption during the 16th World Health Assembly in 1963 of a resolution (WHA 16.36) that reaffirmed the need for early action regarding the rapid dissemination of information on adverse drug reactions (ADRs). This led to the creation of a World Health Organization (WHO) pilot research project with the participation of 10 countries to develop a system that could be implemented internationally to detect the previously unknown or poorly understood adverse effects of medicines.

1.1. Rationale for Action

ADRs, especially those that are serious and fatal, are quite rare and cannot be identified in experimental premarketing studies such as clinical trials. For example, a mild case of skin rash or nausea after taking the painkiller ibuprofen is a well-known adverse effect considered common or very common. It may appear in 1 percent–10 percent of individuals taking ibuprofen. So, even relatively small studies such as clinical trials involving dozens to a few hundred patients can easily detect and characterize these frequent ADRs.

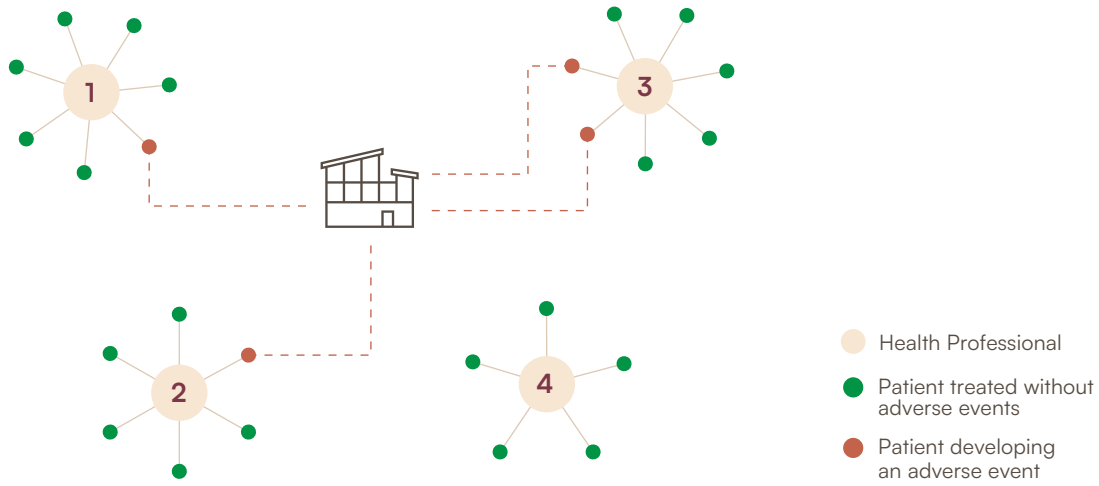
Fortunately, serious or fatal ADRs are much less frequent. A side effect of medicines that is categorized as very rare appears in fewer than 1 case among 10,000 individuals exposed to the causal drug. An example is severe gastrointestinal bleeding after taking aspirin, which could occur in approximately two patients out of 10,000 users of that anti-inflammatory. The drawback is that, because they are such rare events, they cannot be detected if the sample size of a relevant study is small. This explains why these rare but serious ADRs are only detected after thousands of patients have been exposed to the medicine. Because it would be extremely difficult to follow cohorts of 100,000+ patients, the best method for identifying patients presenting these ADRs consists of collaborating with multiple observers who are available to report identified cases to a centralized surveillance unit (figure 1). To improve the knowledge of the safety of medicines, a network of voluntary reporters is the most effective method, and this is the method that has been selected for the global pharmacovigilance (PV) surveillance network.

The first practical international cooperation in drug monitoring was initiated in 1968 to ensure that evidence about harm to patients was collected from as many sources as possible. The initial activities of the pilot project culminated in the current WHO Program for International Drug Monitoring (PIDM), which has grown to become a global network of national PV centers around the world.[1] This network enables individual countries to be alerted to patterns of harm that have emerged worldwide, but that might not be evident from only the local data of a country. Members of the program work nationally and collaborate internationally to monitor and identify the harm caused by medicines, reduce the risks to patients, and establish worldwide PV standards and systems (see figure 1). Pharmacovigilance is the safety monitoring of medicines (box 1).

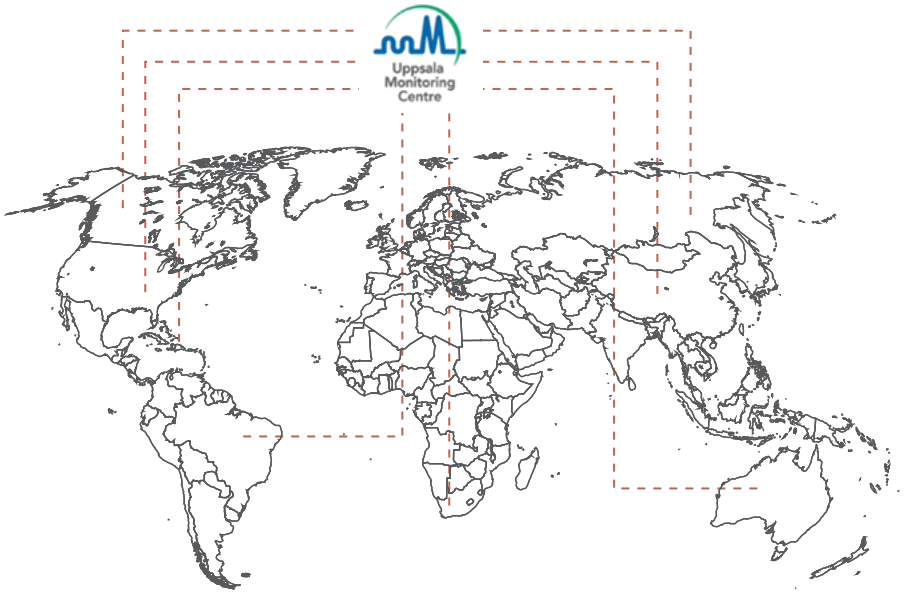
[1] See "The WHO Programme for International Drug Monitoring (PIDM) and How to Join," World Health Organization, Geneva, https://whopvresources.org/who_pidm.php.

Figure 1 Mechanics of Global Pharmacovigilance: Reporting Suspected ADRs

a. Health professional interactions with patients



b. PV center inactions with the PV database



Note: Panel a: Each health professional follows many patients treated with one or more medicines without presenting any ADR. But, if one patient develops an ADR., then the health professional who detects it reports the case to the local PV center. Panel b: Periodically, each local PV center uploads all the received ADR reports to the global PV database, maintained by the Uppsala Monitoring Center (UMC).

Box 1
Pharmacovigilance: A Working Definition

The WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems" (WHO 2002, 7).

This description is an umbrella for multiple elements relating to the safety of medications, including the reporting of substandard and falsified medicines, medication errors, drug abuse and misuse, exposure to medicines during pregnancy and breastfeeding, therapeutic ineffectiveness, occupational exposure, off-label use, ecopharmacovigilance (environmental pollution), medical devices and diagnostics, overdose, and the suspected transmission of infectious agents via medicines (Peters et al. 2021; Viana et al. 2021). It can even be useful in identifying therapeutic failure and antimicrobial resistance (Habarugira and Figueras 2021).

1.2. The Uppsala Monitoring Center

To increase the effectiveness of the search for previously unknown ADRs, all the monitoring activities conducted in health centers and research units worldwide must be somewhat coordinated. The Uppsala Monitoring Center (UMC) has been responsible for the technical and operational aspects of the WHO-PIDM since 1978. As an independent, nonprofit foundation, the UMC works with the WHO and engages stakeholders who share the same vision of advancing the safety of medicines, together with the global pharmacovigilance community.[2]

The UMC is independent and self-funded; the center finances its operations by selling pharmacovigilance products and services to external bodies, most notably the WHO Drug Global portfolio of products. Funding its own operations ensures intellectual and scientific independence, sustainability, and freedom to pursue UMC's vision (UMC 2022c).

1.2.1. Mission

The UMC has the mission to promote rational medicines therapy through the following (Olsson 1998):

- Collecting and analyzing information about drug safety at the international level
- Collecting, classifying, and disseminating information about national activities concerning drug safety
- Developing professional and scientific expertise to improve the analysis of international questions concerning drug safety and developing methods for use in work within drug safety and neighboring fields
- Supporting the development of standards for the assessment of risk and beneficial use of drug therapy
- Contributing to the improvement of communication and education among relevant interest groups concerning the risks and advantages of drug treatment
- Contributing, on request, to the development of methods for international application within fields closely linked to drug safety

[2] See "Get to Know UMC," Uppsala Monitoring Center, Uppsala, Sweden, https://who-umc.org/about-uppsala-monitoring-centre/.

1.2.2. Activities

Within the framework of PV, UMC activities can be summarized as follows:

- *Collection of ADR reports worldwide and maintenance and use of an international database*: the UMC maintains and periodically analyzes VigiBase, the global PV database.
- *Dissemination of information*: in addition to many research articles published in medical journals, the quarterly journal *Uppsala Reports* publishes national information and updates submitted by WHO-PIDM members (UMC 2021a).
- *Education and advice*: One of the UMC pillars consists of developing training to ensure the knowledge and expertise of the health professionals involved in PV. This includes online and live training initiatives covering various topics, from PV basics to the analysis of signals (UMC 2022b).
- *Research and development*: The periodical analysis of the database to identify safety signals is one of the most important objectives of PV. Some of these research activities lead to publications in scientific journals; most of which are collected in the UMC PV library.[3]
- *International harmonization*: The role of international harmonization in pharmacovigilance is highly relevant because the WHO program contributes to the development of common standards and methodologies in the area of medicines safety monitoring chiefly through the following (Olsson 1998):
  - Developing definitions of words commonly used in pharmacovigilance
  - Organizing annual meetings of representatives of national centers in collaboration with WHO headquarters, Geneva
  - Maintaining tools commonly used in drug safety activities (for instance, the WHOART and the WHO Drug Dictionary, tools for the recording of drug safety information)
  - Closely collaborating with other organizations involved in pharmacovigilance (such as the International Society of Pharmacoepidemiology, the International Society of Pharmacovigilance, the Drug Information Association, and the Council for International Organizations of Medical Sciences), and actively taking part in conferences organized by these parties

1.3. Building up the network

The rationale for setting up the WHO-PIDM was to make it possible to identify rare ADRs that cannot be found in the clinical trials conducted during the preauthorization process for the marketing of medicines. In addition, the WHO network represents the wealth of competence and experience that is at the disposal of countries wishing to join the international pharmacovigilance community (Olsson 1998). This results from collaborative work involving many countries, an extraordinary number of health professionals, and even citizens. But to reach this point of maturity has taken more than five decades.

The 10 founding members of the WHO-PIDM in 1968 were Australia, Canada, Czechoslovakia, the Federal Republic of Germany, Ireland, the Netherlands, New Zealand, Sweden, the United Kingdom, and the United States. As of June 2022, the WHO-PIDM is a Global Collaboration Patient Safety Network constituted by 152 full member economies and 21 associated members; this means that PIDM is an initiative covering about 99 percent of the world's population.[4] The full and associate members belonging to the WHO-PIDM can be conferred in the WHO webpage.[5] Some overseas territories may be covered by another full member or benefit from the consolidated PV system of a neighboring country. For example, in the case of Gibraltar, reports are received and analyzed by the UK's Medicines and Healthcare products Regulatory Agency.[6] In the case of Liechtenstein, that country has an agreement with the Swiss PV system (VigiServe Foundation 2020). Box 2 presents the requirements for joining the network.

[3] See "Discover Scientific Publications on Pharmacovigilance," Uppsala Monitoring Center, Uppsala, Sweden, https://who-umc.org/publications-library/research/.

[4] See the website of the WHO Programme for International Drug Monitoring, at https://who-umc.org/about-the-who-programme-for-international-drug-monitoring/.

[5] See https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/pidm.

[6] See the website of the UK Medicines and Healthcare products Regulatory Agency, at https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency.

Box 2
Requirements to Become a Full Member of the WHO-PIDM Network

Participation in the WHO-PIDM network is voluntary and depends on the choice of each country. But, once it has decided to become involved in the international safety surveillance network, a government must officially express its interest and apply to the UMC.

The ministries of health of member countries are required to establish a pharmacovigilance center responsible for the safety of medicines and maintain contact with the WHO in this specific field. Additionally, to ensure that the international data are as up-to-date as possible, member countries are asked to send reports of suspected adverse reactions to the UMC at least every quarter, preferably more frequently. The reports must be submitted in a specific, compatible format, with attention to both the quality and completeness of the data (UMC 2021b). Once countries show that they are ready to fulfill these requirements, they can become full WHO-PIDM members. If a given country is interested in developing PV activities, it may be named an associate member until it is ready to become a full member.

Each country participating in the WHO program appoints a national center. This center is responsible for collecting spontaneously reported suspicions of ADRs. These case reports originate mostly from health professionals; in some countries, citizens may also contribute reports. Additionally, marketing authorization holders must report any suspected adverse event associated with their products and occurring in their country. Then, the national centers regularly transform these case reports into a specific WHO format and periodically submit them to the UMC. At the UMC, reports are checked for technical accuracy and entered into the WHO database (Olsson 1998).

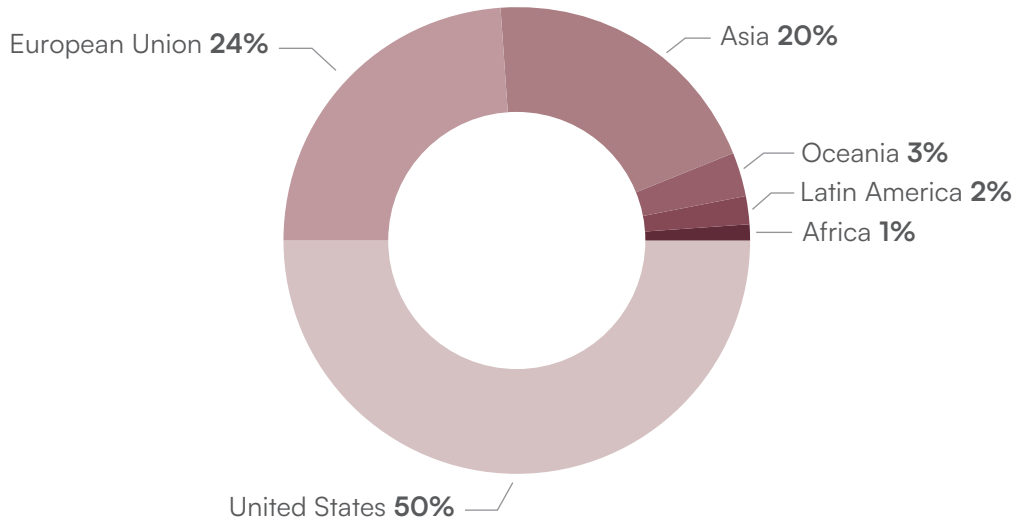
The WHO supports countries in promoting sustainable monitoring systems under the PIDM. The WHO's regional offices support program implementing in low- and middle-income countries to respond to the needs of these economies, while considering intended state-of-the-art pharmacovigilance initiatives (Olsson et al. 2010). Issues related to drug use and adverse event profiles can vary from one country to another because of differences across manufacturing processes, local therapeutic practices, and the population's genetic factors. Every country should therefore develop its own national pharmacovigilance system (Khalili et al. 2020; Pirmohamed et al. 2007).

1.4. VigiBase: the global PV database

Collecting all the information delivered by more than 150 countries requires a robust database. So, in 1978, an initial database at WHO headquarters in Geneva was moved to the UMC. This became VigiBase.

VigiBase is the largest database of its kind globally. It contains records submitted by member countries of the WHO-PIDM dating back to 1968 on the reported potential side effects of medicinal products. Until about a decade ago, the expansion of VigiBase was relatively slow. But an increasing awareness of the importance of global pharmacovigilance—reflected in changes to national and regional laws, regulations, and practice—has led to much higher levels of

Figure 3 Regional Distribution of VigiBase Reports



Source: Based on the analysis of Watson et al. 2019.

reporting and sharing data. In September 2021, the number of reports in VigiBase passed 28 million (UMC 2021c).

An analysis of the more than three million ADR reports from 96 countries added to VigiBase from 2000 to 2009 shows that approximately 85 percent were provided by high-income countries, primarily and Australia, Canada, France, Germany, the United Kingdom, and the United States. Reports from upper-middle-income and lower-middle-income countries constituted 7 percent and 8 percent, respectively, of all reports, and fewer than 1 percent of the reports were supplied by low-income countries (Aagaard et al. 2012).

An analysis of the ADRs on men and women collected within VigiBase up to January 2018 included more than 15 million reports from the 131 member countries of the WHO-PIDM at that time (Watson et al. 2019). Figure 3 shows the regional distribution of these reports.

According to a September 2021 report (UMC 2021c), the contributions to VigiBase were dominated by reports from the United States (which accounted for 45 percent of the data). The European Union contributed another 20 percent. However, the share of reports from Asia rose appreciably: China, India, and the Republic of Korea showed larger shares among the total and in annual contributions.

Other sections of this report describe various case studies covering PV in the Caribbean, the European Union, Brazil, Ghana, India, Korea, Spain, and the United States. So, this situation analysis is a descriptive review focusing on the development and current status of PV in lower-middle-income economies and various regions: Africa, Asia, Latin America, and the Middle East.

2. Pharmacovigilance systems in practice

Globally, over 150 countries have a fully operational PV system. The history, characteristics, challenges, and outcomes of each of these systems are different. The first part of this section (2.1) explains how we can evaluate a PV system and what we have learned from establishing PV systems. Section 2.2 then summarizes the findings of a published overview of PV in 55 countries and describes different regional networks to improve the surveillance of medicines safety. Despite the differences among national PV systems and the variations in the time elapsed since the incorporation of the systems into the WHO-PIDM, high-income countries generally have more mature PV systems because of the resources allocated by and the commitment of governments, the related supranational structures that support the PV work in these countries, and a long history of monitoring medicine safety. This is the case of most European countries, where the European Medicines Agency is harmonizing and supporting the efforts of country members. Additionally, their results and achievements are well known and their safety decisions have been highly publicized. The analysis of the situation in lower-middle-income countries offers a marked contrast that requires additional local and international support to build the PV capacity as an integrated component of a health system.

2.1. Evaluation of country pharmacovigilance systems

Evaluating a PV system facilitates actions to overcome the deficiencies that have been identified and improve the quantity and quality of ADR reports, leading to more rigorous decision-making in pharmacovigilance. In addition, various indicators are used to assess the performance and maturity of country PV programs. Utilizing such measurement tools allows countries to benchmark and compare their performance with counterpart nations and enables quantification of the impact of future public health interventions through policy enhancements to ensure the safety of pharmaceutical products on the market (Qato 2018).

Two commonly used and well-tested indicators were included in the document "WHO Pharmacovigilance Indicators: A Practical Manual for the Assessment of Pharmacovigilance Systems." (WHO 2015) and the document "Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries" (SPS 2009).

2.1.1. Maturity of the WHO-PIDM network

PV in countries is dynamic, evolves, and improves with time. The results obtained by a PV center thus not only depend on the actual number of reports received, but also on the reporting rate per million inhabitants, the amount of time the local PV system is operating, the number of specialized health professionals working in it, the turnover of the staff, and the available funding to deploy the PV program.

The year each country undertook PV activities serves as an indication of the maturity of the local system. Examples demonstrate this heterogeneity and the associated contributing factors.

The example of East Africa: Ethiopia, Kenya, Rwanda, and Tanzania

Abbie Barry and her team conducted a survey to assess the functionality and identify the strengths and limitations of the national pharmacovigilance systems in Ethiopia, Kenya, Rwanda, and Tanzania (Barry et al. 2021).

Ethiopia, Kenya, Rwanda, and Tanzania are all members of the PIDM. Tanzania (Tanzania Medicines and Medical Devices Authority) was the first to join the program, in 1993, followed by Ethiopia (Ethiopian

Box 3

Summary Survey Findings: Four East African Countries

- The national pharmacovigilance programs of Ethiopia, Kenya, Rwanda, and Tanzania were well supported by legal instruments and guidelines.
- New regulations or guidelines aiming to converge with international pharmacovigilance standards are currently being introduced in all four countries.
- Although the local PV institutions enjoy legal support and have established pharmacovigilance systems and structures, limited stakeholder involvement and engagement in the pharmacovigilance systems are manifested in low reporting rates.
- In all four countries, procedures for data collection and management, signal analysis, and decision-making have been instituted or are being introduced. However, at the time of the assessment, the pharmacovigilance systems did not have sufficient capacity systematically to identify new problems among pharmaceutical products occurring in local health care delivery systems.

Source: Barry et al. 2021.

Food and Drugs Authority) in 2008. Kenya (Pharmacy and Poisons Board) and Rwanda (Ministry of Health) joined in 2010 and 2013, respectively.

The survey was based on the East African Community Harmonized Pharmacovigilance Indicators tool, which is derived from the WHO pharmacovigilance indicators and the Indicator-Based Pharmacovigilance Assessment Tool (SPS 2009). The main results are summarized in box 3.

Thus, despite the differences in the duration of operations (since 1993 in Tanzania and since 2008 or later among the others), Barry et all (2021) still find that these PV systems are not yet at full capacity.

As a useful recap, tables 1 and 2 describe the national systems, structures, stakeholder coordination, signal generation, and data management in the four East African countries included in the surveillance.

Table 1 PV Systems and Coordination, Ethiopia, Kenya, Rwanda, and Tanzania

Country	Defined annual budget for pharmacovigilance	Existence of a source of data on consumption and/or prescription of medicines	Pre-service training	In- service training	Web-based training	Communication plan to disseminate pharma-covigilance information	Toll- free number	Website
Ethiopia	✗	✗	✓	✓	✗	✓	✓	✓
Kenya	✓	✗	✗	✓	✗	✓[a]	✗	✓
Rwanda	✗	✗	✗	✗	✗	✗	✗	✗
Tanzania	✓	✗	✗	✓	✗	✓	✓	✓

✓ present, ✗ missing/not available, *NMRA* National Medicines Regulatory Authority, *PPB* Pharmacy and Poisons Board
[a]No specific plan for pharmacovigilance; communication plan available for the NMRA (PPB), but not specific to pharmacovigilance
Source: Barry et al. 2021.

Table 2 Signal Detection and Data Management in East Africa

Country	Existence of a national database for pharmacovigilance information	Existence of standard adverse event reporting form	Existence of standard adverse event reporting form for the public	Existence of electronic adverse event reporting system	Process for collection, recording, and analysis of ADR reports
Ethiopia	✓	✓	✗	✓	✗
Kenya	✓	✓	✗	✗	✗
Rwanda	✓[a]	✓	✗	✓	✓
Tanzania	✓	✓	✓	✗	✗

✓ present, ✗ missing/not available, *ADR* adverse drug reaction
[a]Database was not in use
Source: Barry et al. 2021.

Vietnam: ups and downs before system consolidation

Nguyen et al. (2018) have published an overview of the development and consolidation of PV in Vietnam. The experience of Vietnam offers an example of the ups and downs in the dynamics of some national PV centers and also of one way maturity can be reached.

First steps

In 1994, the country launched its first ADR monitoring center, an experimental center under the National Institute for Drug Quality Control undertaken with financial and technical support from the Swedish International Development Cooperation Agency. In 1999, Vietnam became the 98th member of the WHO-PIDM.

This is what happened soon after that milestone:

- Unexpectedly, in 2004, soon after the Swedish support ended, PV activities decreased significantly, and all ADR reports were forwarded to the Drug Administration of Vietnam.
- From 2004 to 2009, although the drug administration strived to maintain basic PV activities, ADR reporting resulted in no connection or feedback to reporters or health care units, and the drug administration faced many difficulties in database control

and management, especially when the number of reports increased.

- In March 2009, the Ministry of Health launched the university-based National Drug Information and Adverse Drug Reaction Monitoring Center in a significant step toward catching up with international trends (Ministry of Health decision 991/QDBYT). The center is under the management of Hanoi University of Pharmacy and under the direction of the Ministry of Health.
- The center began operations six months later as an important milestone, creating new opportunities to develop drug safety surveillance. In addition, the decentralization of pharmacovigilance activities was approved, and the creation of three regional pharmacovigilance centers was planned in the north, middle, and south of the country (see Prime Minister 2006).
- However, by March 2011, only one regional center had been established (at Cho Ray hospital, Ho Chi Minh City). By 2017, only two centers had collected drug safety information across the entire country and assisted the drug administration in drug regulation activities.
- The Pharmacy Act (2005), which supported PV activities, was strengthened by the revised Pharmacy Act (April 2016), which addressed the specific responsibilities of the various stakeholders in the PV system.

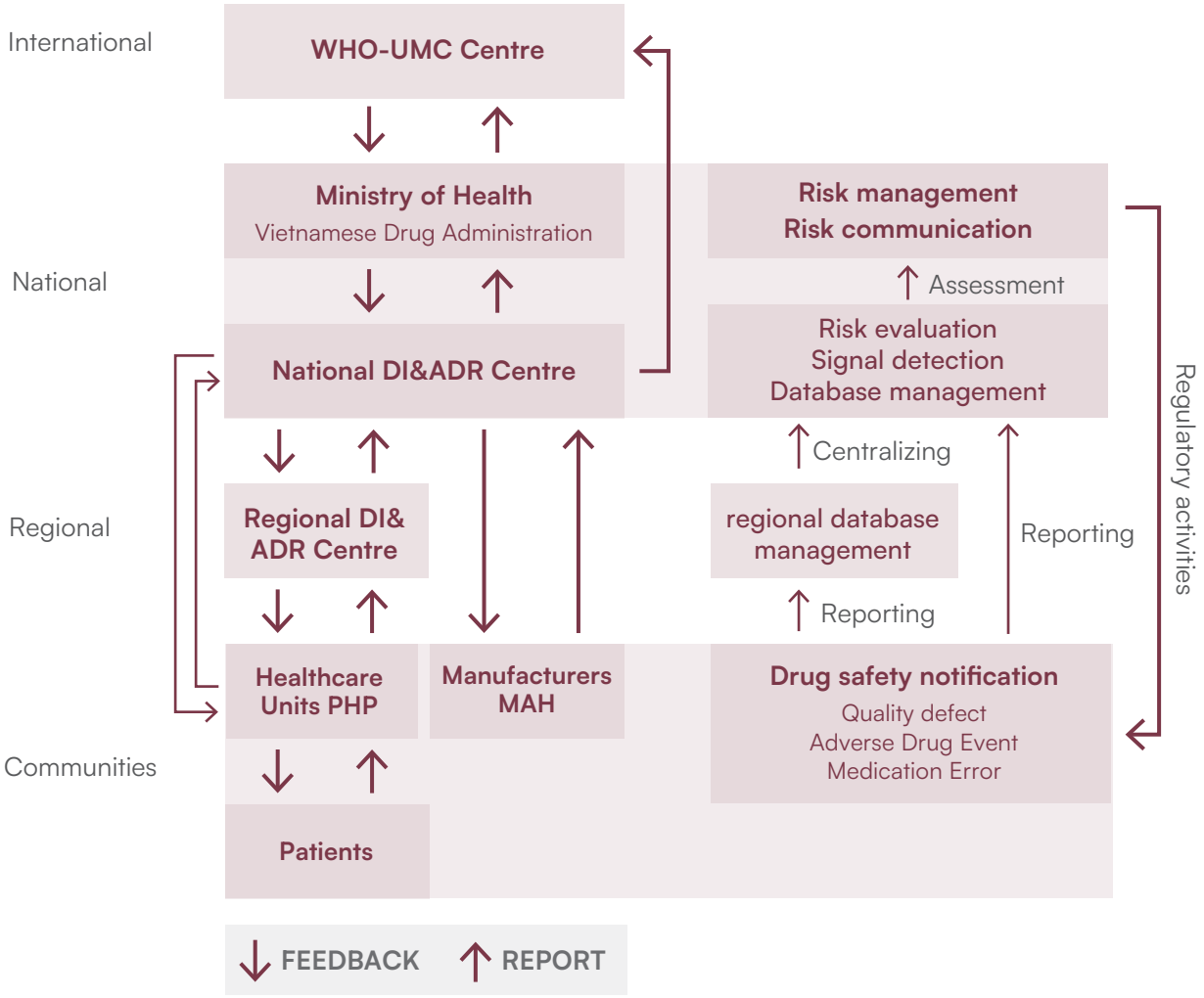
The National Drug Information and Adverse Drug Reaction Monitoring Center is an independent center that has benefited from the well-educated human resources and research capacities of Hanoi University of Pharmacy and from close coordination with the drug regulatory authority in managing all PV activities. The center receives national and international support from the Global Fund to Fight AIDS, Tuberculosis, and Malaria and benefits from increased participation from clinical pharmacists in reporting ADRs. An interactive two-way mechanism between the center and health care units has been created to enhance the quality of the pharmacovigilance process, from signal detection to risk management.

Initial achievements

The analysis supporting this review has quantified some achievements in Vietnam that may promote an understanding of what may be expected from an appropriate investment in PV.

- Within seven years of the establishment of the national information and monitoring center, the quality and the quantity of ADR reporting in Vietnam had increased considerably. From 2010 to 2016, the center officially received 40,031 ADR reports from various sources (health care units, public health care programs, and marketing authorization holders).
- The number of reports has risen rapidly. In particular, reports received between 2014 and 2017 account for more than 70 percent of the total reports received since 2009. This can be explained by the positive attitudes, knowledge, and acceptance of pharmacovigilance among health care professionals. In terms of quality, the completeness score for reports from health care professionals in 2010–14 was relatively better than the international average score.
- Between 2010 and 2015, the Ministry of Health issued several legal documents related to pharmacovigilance: the National Guideline on Pharmacovigilance, specific guidance on reporting ADRs in health care facilities, and a series of technical guidelines on ADR (Trần 2017). Figure 2 depicts the structure resulting from these actions.

Figure 2 Structure of the Pharmacovigilance System, Vietnam



Source: Nguyen et al. 2018.
Note: DI&ADR = drug information and adverse drug reaction monitoring. PHP = public health care programs. MAH = marketing authorization holder. WHO-UMC = World Health Organization–Uppsala Monitoring Center.

Challenges

Identifying challenges helps in planning improvements. The main obstacle faced by the Vietnamese PV system is the remarkable variation in the quality and quantity of reports across regions, hospitals, and subgroups of health care professionals (that is, physicians, pharmacists, nurses).

- Until 2016, only 805 of 13,617 health establishments (fewer than 6 percent) had participated in reporting activities. The imbalance was worse in remote areas because of a lack of highly qualified health care professionals. Furthermore, the burden of work in health care centers and differences in knowledge, attitude, and practice had led to underreporting. Pharmacovigilance might still be unfamiliar to most health care workers despite the official National Pharmacovigilance Guideline promulgated in June 2015.
- Reporting activities were considered routine practice in HIV/AIDS, tuberculosis, and malaria programs. Still, this integration was difficult to maintain because of a lack of direct government support and clear institutional instructions.

- The Drug Administration of Vietnam registers vaccines and herbal medicines, but the supervision of vaccines in the community is mainly performed through the Department of Preventive Medicine (an administrative unit in the Ministry of Health), while the control of herbal medicines is under the Traditional Medicine Administration (also an administrative unit in the Ministry of Health). Lack of effective communication between these units has sometimes proven to be a barrier to pharmacovigilance. Safety issues related to vaccines may lead to rumors, possibly damaging overall confidence in vaccination and dramatically affecting immunization coverage and disease incidence.
- Drug safety is the responsibility of the PV centers, the Ministry of Health, and the community. Reporting by private pharmacies and patients should be considered appropriate parts of the pharmacovigilance system. Support and a clear strategy exercised by the national authority are needed to deal with this issue.

PV in Iran: the issue of underreporting

Underreporting and low-quality reporting are major limitations of PV systems because the method's effectiveness requires trying to capture as many ADRs as possible by observers in primary care and hospital facilities. Underreporting is an issue in almost all PV systems, and this example in Iran highlights the causes.

The Pharmacovigilance Center of Iran launched activities under the supervision of the Iran Food and Drug Administration in 1991. It then became a full member of the WHO-PIDM in 1998. In the first 10 years of center activity, the underreporting of ADRs was a common drawback (Shalviri, Valadkhani, and Dinarvand 2009).

The center is supported by a national policy, trained staff, and a statutory budget. In 2017, the number of ADR reports was 15 per 100,000 population, and 262 signals were detected during the preceding five years (Khalili et al. 2020).

The main causes of underreporting in Iran are lack of awareness of the existence of the national center and its functions, inadequate knowledge about reporting, and fear of punishment and criticism (Afifi et al. 2014; Mirbaha et al. 2015). The system's current status and efficiency are unknown, and there is little adequate systematic data on the effectiveness and functionality of the center.

Khalili et al. (2020) analyze the WHO indicators on the country. They find that, despite the existence of a functioning PV structure and resource, policy, and regulatory framework, the performance and achievements of the Iranian PV program require suitable and sustained improvement. However, "the state of completeness and causality assessment of the reports was satisfactory, and the PVC [the center] of Iran had appropriately utilized statistical methods to help detect signals from the ADR reports" (Khalili et al. 2020, 5).

- The status of structural indicators on Iran's PV program demonstrated a relatively satisfactory commitment to improving medication safety and providing direction to enhance the system.
- This program had a statutory budget and limited human resources to function.
- The absence of PV in the training curriculum among health care professionals in Iran suggests their lack of preparedness for career challenges in medicine safety issues.

Limited budgets and the lack of trained personnel are two reasons for low performance in PV programs. However, it is a quite common problem, shown by Qato (2018), in the region that is also highlighted by Olsson and his colleagues in their classical analysis of PV in 55 lower-middle-income countries (Olsson et al. 2010). Table 3 shows an example of the analysis of structural indicators to identify weak points in a system.

Table 3 Analysis of WHO Core Pharmacovigilance Structural Indicators, Iran

Assessment Indicators	Answers	Description
1. Existence of a pharmacovigilance center, department, or unit with a standard accommodation	Yes	Center for the registration and reporting of health products' safety and adverse effect, with non-standard accommodation (a small office space, the shortage in some basic office equipment and facilities required to receive, analyze and transmit ADR reports).
2. Existence of a statutory provision (national policy, legislation) for pharmacovigilance	Yes	• Guidelines for registration of ADR and medication errors reporting with the signature of the Minister of Health (available at: https://www.fda.gov.ir/en): as a mandatory policy in the Iranian FDA. • Legal commission vote on manufacturing and import of medicines in 2005.
3. Existence of a medicines regulatory authority or agency	Yes	Department of Assessment and Control on Prescribing and Use of Medicines and Health-related Products.
4. Existence of any regular financial provision (eg, statutory budget) for the pharmacovigilance center	Yes	The annual budget for interventions and activities such as education about ADR reporting and pharmacovigilance, holding workshops and training courses, implementing related projects, and empowering regional pharmacovigilance centers.
5. Existence of human resources to carry out its functions properly for the pharmacovigilance center	Yes	There was a shortage of human resources (only 5 pharmacists and physicians).
6. Existence of a standard ADR reporting form in the setting	Yes	Yellow ADR form and online system for ADR and medication error reporting: https://adr.ttac.ir
6a. The standard reporting form provides for reporting: suspected medication errors, suspected counterfeit/ substandard medicines, therapeutic ineffectiveness, suspected misuse, abuse of and/or dependence on medicines, ADRs by the general public	No	Only the Yellow ADR form is available, and all drug-related problems are reported by this form. Moreover, the general population could report ADR via website: https://adr.ttac.ir
7. Existence of a process in place for collection, recording, and analysis of ADR reports	Yes	Reports of suspected ADRs submitted voluntarily to a regional center or the national regulatory authority by healthcare professionals or patients via completing the yellow card, e-mail, telephone, fax, or online website. Finally, all reports are assessed and analyzed by the staff of PVC.
8. Incorporation of pharmacovigilance into the national curriculum of the various healthcare professions (medical doctors, dentists, pharmacists, nurses or midwives, and others)	No	Pharmacovigilance has not been incorporated into the national curriculum of the various healthcare professions.
9. Existence of a newsletter, information bulletin and/or website as a tool for dissemination of information on pharmacovigilance	Yes	Dissemination of information via https://www.fda.gov.ir/en
10. Existence of a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety	Yes	Predominantly physicians and pharmacists serving as members of this committee and have 5 main members. They hold their meetings occasionally.

Source: Khalili et al. 2020.
Abbreviations: WHO, World Health Organization; ADR, adverse drug reaction; MoH, Ministry of Health; PVC, Pharmacovigilance Center.

The key messages of their analysis of the PV program in Iran include a few ideas that seem to be quite common in various lower-middle-income countries (Khalili et al. 2020):

- Usually, PV programs need suitable and sustained improvement despite a basic PV structure, resource, policy, and regulatory framework.
- In the example of Iran, the system requires the higher prioritization of PV in public health programs and a greater allocation of resources to bolster the system and achieve the country's objectives in safety monitoring.
- The suitable and sustained promotion of a PV program can be facilitated by improved collaboration with professional organizations, including participation in educational events and scientific meetings.

2.1.2. Establishing PV systems: what we have learned

Sten Olsson and his team from the UMC published a review on PV in economies with limited resources countries after five years of activity (Olsson, Pal, and Dodoo 2015) (box 4). One key message is that "every country is unique, and there is no general recipe on how to establish a PV system in a country" (Olsson, Pal, and Dodoo 2015, 450). Nonetheless, the review highlights common features of the development of PV that are important in planning actions for the establishment or strengthening of programs.

Box 4

Common Features of PV Development in Limited-Resource Economies

- PV is often initiated by a few dedicated health care professionals who observe treatment-related harm in patients. They take it upon themselves to introduce a reporting and learning system in their environment to minimize 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 the systematic collection of observations of suspected medicine-related harm.
- PV activities invariably start with the spontaneous reporting of individual case safety reports because this is the least resource-demanding method that may be initiated without major investment.
- Country authorities often apply for formal training in the PV methodology during the early implementation phase, such as the training offered by the WHO-PIDM through network collaborating centers, professional associations such as the International Society of Pharmacovigilance, or a limited number of academic institutions. An alternative way of learning PV basics is through internships in well-established PV centers.
- Some country authorities only start PV as part of a regional or subregional initiative involving economic communities, such as the Economic Community of West African States or the East African Community. In these settings, one or two country actors take the lead in establishing PV centers, which are often used by the others for contacts, learning, and capacity building.

Source: Olsson, Pal, and Dodoo 2015.

Olsson Pal, and Dodoo (2015) also reflect on budgetary aspects and the difficulties of rendering the principal PV activities sustainable. Although country authorities may benefit from regulatory provisions in establishing PV systems, only when these provisions are matched with a regular and sustainable budget can real action and long-term planning be achieved. Good examples exist in countries such as China and India. In India, initiatives have been taken by various academic and research institutions and the regulatory authority to establish PV in the country since the mid-1980s. However, only when the government created a budgeted staff position for PV in 2010 was the PV system effectively established in the whole country (Biswas 2013; also, see below). In China, the government invested heavily in PV training in the provinces, leading to a rapid increase in the submission of individual case safety reports to the National Coordinating Center (Zhang et al. 2014).

In summary, the WHO, through UMC activities, has a major role in harmonizing the safety monitoring programs of the 152 full members, defining standards, training and updating the network of health professionals, taking advantage of the information uploaded to the common database, contributing to the signal detection process, and making collaborators aware of new safety concerns.

Despite this harmonizing role, the WHO-PIDM is the fruit of the contributions of 152 countries with different characteristics, heterogeneous human and financial capacity, and diverse experiences, backgrounds and interests in (1) detecting and reporting suspected ADRs, (2) analyzing the received reports to contribute identifying signals, and (3) using the country PV activities to disseminate information on safety issues and improve the use of medicines and vaccines, thereby preventing or reducing ADRs among others.

The next sections of the Situation Analysis detail how PV is evolving at the regional level.

2.2. Overview: pharmacovigilance in 55 countries

Perhaps the most comprehensive assessment of the performance of national PV systems was a classical study conducted by Sten Olsson and his UMC team (Olsson et al. 2010). Although the panorama has changed a lot in the last decade, examining the results of the study is useful.

The aims of the survey were as follows:

- Assess current and planned pharmacovigilance activities
- Identify gaps and the most urgent PV priorities at the national and international levels and define the elements of a sustainable global pharmacovigilance strategy

Fifty-five countries completed the questionnaire; almost half the PV centers were established during the 1990s, and the other half were set up later. These PV centers were affiliated with their Drug Regulatory Agency (69 percent), with the Ministry of Health (20 percent), or with a university or scientific body (9 percent) in a high proportion of these countries (n = 42).

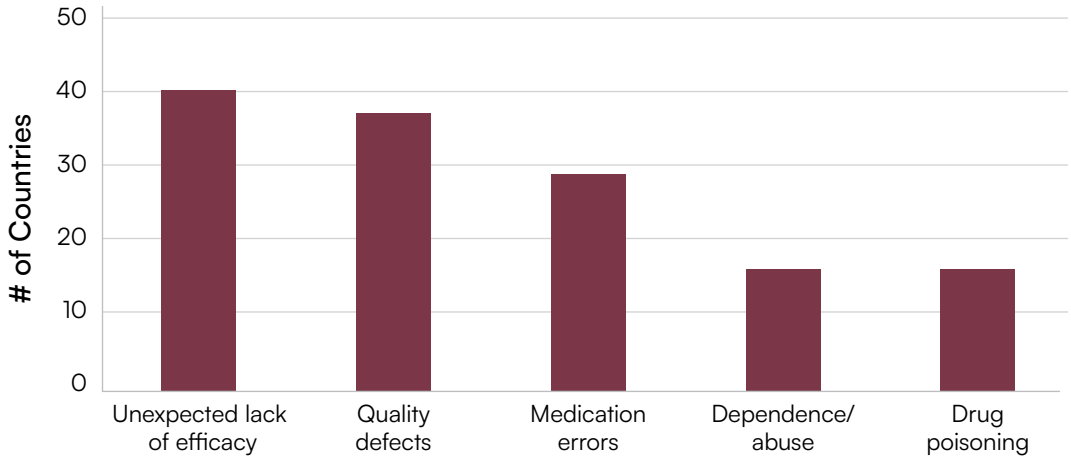
Table 4 illustrates the consequences of PV activities in these countries, measured as the number of regulatory actions that are the consequence of the safety monitoring results.

Table 4 Regulatory Actions Based on PV Activities, 2007

		No. of times action taken		
Action taken	**No. of countries taking action**	**once or twice**	**three or more times**	**not stated**
Safety warnings	24	13	9	2
Changes of product information	21	8	7	6
Suspension/withdrawal of drug product licence	20	7	7	6
None of the above	15			

Source: Olsson et al. 2010.

Figure 4 Additional Problems Reported through Pharmacovigilance Centers



Source: Olsson et al. 2010.

Many PV centers were also involved in other activities, such as drug information (63 percent), promoting patient safety (52 percent), fostering the rational use of drugs (46 percent), and disseminating poison information (15 percent). In addition, seven countries had sentinel sites to monitor HIV/AIDS patients and other special groups. Figure 4 illustrates how some of these PV centers contribute to detecting other medication-related problems beyond the side effects of treatments, especially lack of efficacy, quality defects, or medication errors.

Few countries (23 of 55) have any budget allocated for pharmacovigilance.

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), Management Sciences for Health (18 percent), and the rational use of drugs networks (15 percent).

Lack of training and funding were mentioned as major challenges to pharmacovigilance in many countries.

"While all but seven of the responding countries indicated the presence of a designated pharmacovigilance program, considerable variations and gaps exist in the pharmacovigilance infrastructure, resources, and methodologies."

—Olsson et al. 2010

The results of that survey, conducted with the participation of the UMC, helped identify strengths and weaknesses and plan future actions.

"A pharmacovigilance strategy for low- and middle-income countries needs to ensure reasonable economies of scope, that is, it needs to help build a system that can serve the purpose of multiple health conditions using some criteria to prioritize questions that meet a country's specific needs.

"It needs to identify and implement feasible systems, governance, infrastructures, human resource, training and capacity building, sustainable methodologies, and innovations; a key component will be the dissemination of medicines safety information to policy makers and regulators and knowledge sharing through high-quality informatics and learning tools. In its narrower objective, a pharmacovigilance strategy should enable better use of adverse events data, thereby promoting a more evidence-based approach to policy making and treatment guidelines. Capturing comprehensive data as a source of learning and the basis for preventive action is a cornerstone of improving patient safety.

"Thus, in its broader remit, the pharmacovigilance strategy needs to contribute to the coordination of an extended role for population-based pharmacovigilance in improving patient care through actionable learning."

—Olsson et al. 2010.

2.3. Regional networks: a strategic support

The commitments of countries and the support of the WHO UMC, other agencies, and funding stakeholders contribute to the strengthening of national PV systems. But another factor has an important role: the regional support by supranational organizations. Regional involvement has various characteristics and is driven by different organizations, although the aims are similar: harmonization, training support, and regional analysis of specific signals.

This section reviews PV activities in Africa, the Association of Southeast Asian Nations (ASEAN), Latin America and the Caribbean, and the Middle East. It also details the involvement of the African Medicines Regulatory Harmonization (AMRH) Initiative and Pan American Network for Drug Regulatory Harmonization (PANDRH) initiatives.

2.3.1. African economies

The involvement of African countries in PV was first analyzed extensively in 2016. The first factor to be considered is the duration of the PIDM engagement of countries. Following the start of the WHO-PIDM by 10 member countries in 1968, it took another 24 years for the first two African countries to join, in 1992, by which time the number of member countries in the PIDM had grown to 33 (Ampadu et al. 2016) (box 5).

Box 5

The Steady Growth in African PIDM Members Since 2000

With increased access to medicines, the need to monitor medicines safety has become obvious.

- The Global Fund to Fight AIDS, Tuberculosis, and Malaria, for instance, insisted on the safety monitoring of all its products as a key requirement for grant recipients as early as 2002; however, this was only partially adhered to. As a result, the fund included a mandatory field relating to PV on all grant application forms in 2010.
- WHO headquarters, the UMC, and the WHO Collaborating Center for PV in Rabat, Morocco, undertook a focused approach to building PV capacity in Africa. As a result, UMC alone trained 100 Africans in its annual PV course beginning in 1993.
- The United States Agency for International Development, working especially with Management Sciences for Health, also supported PV activities in Africa.
- However, the most direct impact on countries joining the PIDM was the establishment of an African hub to lead PV development on the continent. In June 2009, the UMC established an African office (UMC—Africa) with dedicated funding, while the WHO designated the University of Ghana (October 2009) as a WHO Collaborating Center for Advocacy and Training in Pharmacovigilance, working hand-in-hand with UMC—Africa.

The African hub—the WHO collaborating center and UMC—Africa—undertook advocacy, country visits, and training and capacity building in several countries, culminating in most of them becoming full PIDM members. The rapid increase in the number of African countries joining the PIDM beginning in 2009 was due mainly to this focused continental effort.

Source: Ampadu et al. 2016.

PV was not a priority in Africa before 2000 for several reasons, including poor legislation on medicines regulation, lack of access to medicines and health commodities, weak and uncoordinated supply chains for medical products, lack of knowledge and awareness of PV, and lack of financial, human, and technical resources for PV. But the panorama changed a bit, together with a concerted effort to increase access to medicines in Africa to manage priority communicable diseases, such as HIV/AIDS, malaria, and tuberculosis. In addition, the emerging middle class can pay out of pocket for medical care, especially for noncommunicable disease. Both changes shifted the national development agenda toward the safe and cost-effective use of these products and the establishment of surveillance systems for safety, effectiveness, and quality (Ampadu et al. 2016).

In 2011, of the 46 countries in Sub-Saharan Africa, 25 (54 percent) had minimal or no pharmacovigilance capacity. Furthermore, only 4 countries among these 46 countries (9 percent) had pharmacovigilance systems with the capacity to detect, evaluate, and prevent safety issues, indicating the limited capacities of these countries to monitor medicines safety (Barry et al. 2021).

The situation started improving with the support of the UMC and other stakeholders. An indicator of this change is the reports originating in the new African member states that started to be regularly uploaded to VigiBase. All these reports were uploaded to VigiBase and started contributing to the global database. Though the report submission rate was lower in Africa than in other regions, the findings showed that the reports mirrored the reality of the population, the epidemiology, the interests of the various donors and stakeholders, and the characteristics of the health care system (box 6).

Box 6

What Had African Countries Reported to VigiBase by 2016?

- The number of African countries in the PIDM was 35.
- The cumulative number of reports submitted to VigiBase by these countries was 103,499 (0.88 percent of global reports).
- The main class of suspected medicines in these reports were medicines used in the treatment of HIV infections (28.6 percent), the combinations of antibiotics sulfonamides + trimethoprim (almost 3.0 percent), and angiotensin-converting enzyme inhibitors used in hypertension (2.4 percent). These medicines were completely different from the main product classes implicated in the reports received from the rest of the world.
- The 18—44 age-group dominated in the reports from Africa, while the 45—64 age-group dominated in the rest of the world.

Source: Ampadu et al. 2016.

Harmonization of pharmacovigilance systems in Africa

Since 2009, the AMRH initiative has served as a foundation for the African Medicines Agency. "The AMRH initiative was established to strengthen medicines regulation in Africa by promoting the effectiveness, efficiency, transparency, and collaboration of regulatory mechanisms in these settings" (Kiguba, Olsson, and Waitt 2021).

In 2009, Ghana began to host the WHO Collaborating Center for Advocacy and Training in Pharmacovigilance, promoting PV uptake by ministries of health and other stakeholders across Africa (Isah et al. 2012). This had a major impact on the development of PV in Africa. The training was provided in English by people with a local perspective, but it excluded francophone countries in Africa. In 2011, Morocco began hosting the WHO Collaborating Center for Strengthening Pharmacovigilance Capacity in the Eastern Mediterranean, Francophone, and Arab States. This has enabled numerous patient safety-related research and training activities, including the PV of medication errors, herbal medicines, and vaccines (Kiguba, Olsson, and Waitt 2021).

The current panorama

The comprehensive review conducted by Kibuga and his team was published in 2021; so it depicts the present panorama (Kiguba, Olsson, and Waitt 2021).

- In Africa, 54 of the 55 countries have established national medicines regulatory authorities or administrative units that perform all or some of the relevant functions, albeit with differing growth, expertise, and maturity levels. Of these authorities, 87 percent lack functional pharmacovigilance systems (Ndomondo-Sigonda et al. 2017).
- None of the African authorities has reached WHO Global Benchmarking Tool maturity level 4. In Sub-Saharan Africa, only the national medicines regulatory authorities in Ghana and Tanzania are at maturity level 3, which identifies stable and well-functioning systems (WHO 2022).
- In 2016, the African Union Model Law on Medical Products Regulation was endorsed to promote medicines regulatory harmonization and collaboration in Africa (AUDA-NEPAD and PATH 2016a). One of the five key tenets of this legislative framework is the harmonization of the requirements and processes for ensuring safe medicines in Africa (AUDA-NEPAD and PATH 2016b).[7] This model law was developed and promoted by the Africa Union Development Agency–New Partnership for Africa's Development (Mwangi 2016).
- In 2019, the African Union Assembly adopted the African Medicines Agency treaty, which each member state is expected to sign and then enact a corresponding national law to implement the treaty. Rwanda was the first African Union member state to sign the treaty, in 2019, and 16 other member states subsequently signed (Ncube, Dube, and Ward 2021).
- Only five member states had ratified the African Medicines Agency treaty as of mid-2020 (AMRH 2020).

2.3.2. Asia and ASEAN countries

The ASEAN members are Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. ASEAN covers a geographical area with more than 600 million inhabitants.

There is no integrated action in the region to harmonize and support the strengthening of national PV systems. However, initial steps on pharmaceutical harmonization have already been taken, together with ASEAN health care integration and the activities of the Pharmaceutical Product Working Group. According to some experts, pharmacovigilance systems equivalent to the system of the European Medicines Agency will emerge in Asia in coming years if there is strong leadership from stakeholders, including governments and pharmaceutical companies.[8]

[7] Also see "AU Model Law on Medical Products Regulation," New Partnership for Africa's Development, Midrand, Johannesburg, South Africa, https://www.nepad.org/publication/au-model-law-medical-products-regulation.

[8] "ASEAN Countries Will Lead Asian Pharmacovigilance Harmonisation," interview with Suzette H. Lazo, Pharma IQ, https://www.pharma-iq.com/regulatorylegal/interviews/asean-countries-will-lead-asian-pharmacovigilance.

A survey was conducted to review PV development and the status of signal detection tools in the ASEAN countries. It also compared the findings in these countries against findings among more established agencies in Australia, Canada, Japan, Korea, Switzerland, the United Kingdom, and the United States (Chan, Ang, and Li 2017).

Nine of the 10 ASEAN countries have conducted PV studies. Myanmar had not launched PV when the study was conducted, and it was not included. However, all countries had a PV framework that shared broad similarities in general structure. As a result, the following results were found:

- Regarding official structure, 15 countries, except Lao PDR, had a designated center, department, or unit specifically dedicated to PV activities. While Lao PDR does not have a dedicated center, PV activities are subsumed as part of drug regulatory activities.
- Most countries (except Cambodia and Lao PDR) mandated ADR reporting by companies. Reporting by health care professionals has been mandated only by some countries in Asia and elsewhere, namely, Indonesia, Japan, Korea, Malaysia, the Philippines, Switzerland, and Vietnam. Doctors and pharmacists are required to report ADRs in Switzerland, for comparison.
- As a basic framework, all countries monitored the safety profile of pharmaceuticals, including biologics and vaccines. In addition, most extended the safety monitoring to other health products, such as cosmetics, health supplements, traditional and herbal medicines, and medical devices. This indicates that all countries are fully aware of the gatekeeper role of ADR monitoring in public health.
- Concerning the volume of ADR reporting, the median of 47 ADR reports per year per million population in the nine ASEAN countries was lower than the non-ASEAN countries and the rest of the countries in the WHO database.
- Regarding the capacity to analyze ADR data effectively, all nine ASEAN countries and seven non-ASEAN countries had a system for handling ADR reports.
- However, some countries experienced constraints in human resources; so it was difficult to handle a large number of signals. This was especially relevant in a country such as Singapore, which was facing the challenge of receiving a huge quantity of ADR reports beyond evaluator capabilities in individual review (Lundin 2016).

Pharmacovigilance in Asian countries includes success stories. Other chapters describe in detail the case studies of India and Korea.

2.3.3. The Middle East

Some initiatives, such as the Gulf Health Council or the Gulf Central Committee for Drug Registration, can be the starting point for pharmaceutical harmonization in the Middle East and coordinated actions in PV.

The situation of PV in the region can be analyzed through a few descriptive studies.

PV in the Middle East

The UMC Assessment of Country Pharmacovigilance Situation questionnaire was adapted, translated into Arabic, and administered to the heads of relevant centers responsible for medication safety in 13 Arabic-speaking Middle Eastern countries (Wilbur 2013). The main results are as follows:

- Six countries had implemented formal national pharmacovigilance programs (the Arab Republic of Egypt, Iraq, Jordan, Oman, Saudi Arabia, and the United Arab Emirates). Five (Bahrain, Kuwait, Qatar, West Bank and Gaza, and Yemen) reported no active program or designated center.
- Most were funded by the government, but claimed that staff resources were constrained, ranging from 2 to 10 people.
- Among the programs, 67 percent facilitated the submission of spontaneous ADRs to the center by email, but none directly through a web-based platform.
- All used the information for drug regulatory purposes, and five reported dissemination of safety information to the public.

Oman's program is the oldest in the region, with over 15 years of experience in conducting postmarketing surveillance activities. The center in Saudi Arabia started operations in 2013 under the Saudi Food and Drug Authority. It was the largest such body in the region. Its formal mission included responsibility

to ensure the safety, quality, and efficacy of drugs by developing and enforcing an appropriate regulatory system.

It has been suggested that these two PV centers could serve as important resources for neighboring governments and stakeholders wishing to establish national systems, especially given that the human resources devoted to this task were relatively small in most countries. Additionally, the Gulf Central Committee for Drug Registration was established with a stated mission to unify efforts through various health initiatives, including providing safe and effective medications at reasonable prices in the Gulf states (Wilbur 2013).

The Arab and Eastern Mediterranean region

In 2015, Arab and Eastern Mediterranean countries contributed only 0.6 percent of the 2.1 million suspected case reports to VigiBase, reflecting general conditions of low participation in the reporting of adverse drug events.

A study describing the current state of PV systems in Arab and Eastern Mediterranean countries was conducted between May and September 2015 (Qato 2018). The study survey included more countries than those previously analyzed, namely, Mediterranean countries (Algeria, Lebanon, Libya, Morocco, and Tunisia), predominantly Islamic countries in South Asia (Afghanistan and Pakistan, as well as the Islamic Republic of Iran), and the African region (the Comoros, Djibouti, and Sudan) (Wilbur 2013). Qato justifies the selection of these countries because, "although the Arab and EM [Eastern Mediterranean] region is heterogeneous, and each country has a unique set of social, economic, development, and geopolitical characteristics, there are shared linguistic, historical, and cultural traits that make a holistic account of the state of pharmacovigilance in the region a useful endeavor to inform targeted future interventions" (Qato 2018, 211).

The findings suggested that there were "wide disparities in pharmacovigilance systems in the region, underscoring the need for a multistakeholder effort in bolstering program development and the necessity to build collaboration regionally and internationally to enhance capacity, improve public and health care provider awareness, and assist in the development of pharmacovigilance systems still in their nascent stage" (Qato 2018, 210).

In most cases, countries that performed well in one domain performed well in other domains. This suggests the need to holistically address each country's policy and programmatic gaps based on available resources and infrastructure. "Furthermore, while Egypt and Morocco performed very strongly in the survey, with Egypt achieving the maximum possible pharmacovigilance performance score, there is still much room for improvement" (Qato 2018, 215). For example, the underreporting of ADRs should be addressed.

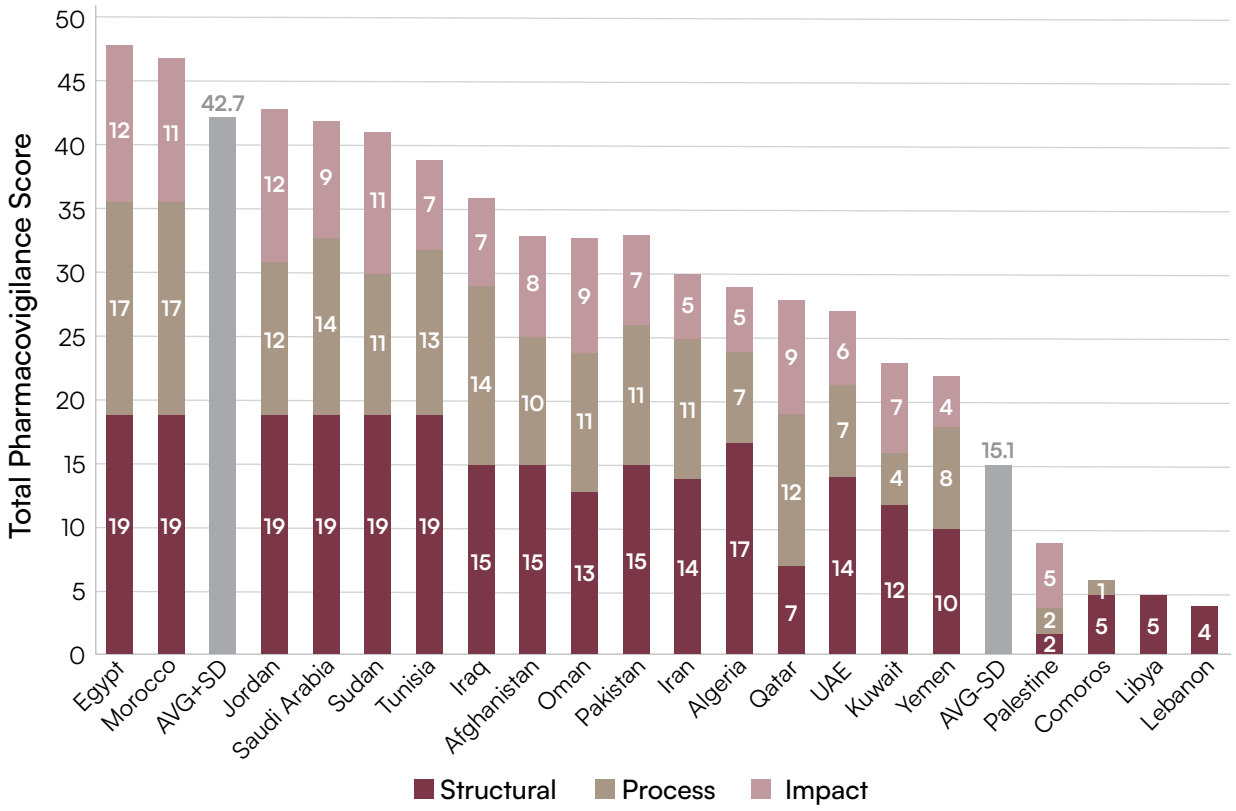
The results can be summarized as follows (Qato 2018):

- More than three-quarters (17) of the 22 countries reported that a formal PV program or policy had been instituted. However, of these 17 countries, only about a third had a budget specifically earmarked for activities related to pharmacovigilance, and 75 percent had a workplace specifically dedicated to pharmacovigilance activities and at least one full-time staff member involved in pharmacovigilance activities.
- Only six countries (30 percent of the sample) had met the minimum requirements for a functional national pharmacovigilance system: Egypt, Jordan, Morocco, Saudi Arabia, Sudan, and Tunisia. "Given the infrastructure required for pharmacovigilance activities and the budget constraints within which (most) countries in the sample operate, especially concerning public health programming, this low performance on pharmacovigilance is not surprising" (Qato 2018, 217).
- In more than 70 percent of the countries with full-time staff devoted to pharmacovigilance activities, total staff members were fewer than seven. "This situation reflects the triple challenges of lack of human capital capacity, inadequate resources devoted to drug safety efforts at the national level, as well as the low prioritization of PV within the public health agenda of some countries in the Arab and EM [Eastern Mediterranean] region" (Qato 2018, 218).

- ·Countries that have made considerable progress over the years and have comparatively more human resources, such as Egypt, Saudi Arabia, and Tunisia, have established PV centers dating back to 1984 (Tunisia). They have made substantial investments at the national level. In Saudi Arabia, this investment has included significant financial backing from the Ministry of Health (Aljadhey et al. 2015).
- Central to developing a robust PV system is the presence of trained health professionals and the capacity to employ them. In several countries in the region, there is a shortage of highly qualified PV professionals.

Alshammari et al. (2019) describe the situation of PV systems in Arab countries. The main message is that Arab countries in Asia have some advantages over those in Africa because 50 percent of the former are part of the Gulf Cooperation Council, indicating that most of them can utilize similar approaches in the majority of activities related to the health care system, including pharmacovigilance. Participation in the Gulf Cooperation Council thus enables closer connections among these countries. However, one of the strengths in Africa is that Morocco is partnering with the WHO through the WHO Collaborating Center to enhance and strengthen pharmacovigilance across the Eastern Mediterranean and among francophone and Arab countries.

Figure 5 PV Survey Results, Arab and Eastern Mediterranean Region, 2015



Source: Qato 2018.
Note: The figure shows the total survey score on pharmacovigilance structural, process, and impact performance.
n = 20 countries.

2.3.4. Latin America and the Caribbean

The Pan American Health Organization (PAHO) has published a comprehensive document on the regulatory system in the Americas (PAHO 2022). This document includes an overview of the development and achievements of PV in the region. In addition, the progression of many national PV systems in the region toward maturity can be explained by the activities of the PANDRH.

The role of the PANDRH in PV and postmarketing surveillance in the Americas

Strengthening the regulatory system has been a priority since the establishment of the PANDRH in 1998. PAHO member states work together to support regulatory harmonization and convergence. They agreed in 2006 to the development of a qualification system coordinated by PAHO to help establish mechanisms for cooperation and recognition across national regulatory agencies (NRAs) (PAHO 2020).

In Latin America, NRAs have substantially advanced the development of PV and postmarketing surveillance systems in the past decade through PANDRH. Between 2008 and 2010, for example, the PANDRH pharmacovigilance working group developed a set of good PV practices for the Americas (PAHO 2011).

Since 2017, one of PANDRH's core activities has been the establishment of two networks of focal points throughout the Americas to exchange PV and substandard and falsified information and conduct collaborative projects. For example, NRAs in Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Mexico, Paraguay, and Peru have participated in joint evaluations of PV documents, such as risk management plans and periodic safety update reports. These evaluations prioritize strategic products with gaps in their safety profiles and biologicals and molecules with specific critical risks. Postmarketing surveillance activities facilitated by the PANDRH focal points include the rapid dissemination of product safety alerts and investigations into clusters of cases in the region.

Box 7

National Regulatory Authorities of Regional Reference in the Americas

In the Americas, NRAr refers to national regulatory agencies (NRAs) that have been assessed by PAHO and found to be competent and efficient in the performance of the health regulation functions needed to guarantee the safety, efficacy, and quality of medicines. This grouping meets regularly in person or virtually to share strategic updates on challenges and important initiatives.

PAHO recognizes eight NRArs in the Americas:

- The National Administration of Drugs, Foods, and Medical Devices, Argentina
- The Brazilian Health Regulatory Agency, Brazil
- Health Canada, Canada
- The Public Health Institute of Chile
- The Colombia National Food and Drug Surveillance Institute, Colombia
- The Center for State Control of Drugs and Medical Devices, Cuba
- The Federal Commission for the Protection against Sanitary Risks, Mexico
- The Food and Drug Administration, United States

Together, these NRArs cover 82 percent of the population of the Americas.

Source: PAHO 2022.

Legal provisions

Legal provisions for PV of medicines, including vaccines, exist in all Latin American national regulatory authorities of regional reference (NRAr) countries.

- NRArs are legally required to establish a reporting and monitoring system to collect adverse drug event data in standardized terminology and to use this information to take regulatory action where appropriate.
- In the case of serious adverse effects associated with vaccines, all NRAr countries have established procedures or norms for coordinating their investigation and subsequent action with national immunization programs, which is often perceived as a challenge in non-NRAr countries throughout the Americas (PAHO 2022).
- All Latin American NRArs are based on legal provisions requiring marketing authorization holders to have a PV system to monitor product safety and report results to the NRAs. In all cases, the NRAs have the authority to inspect the marketing authorization holder.

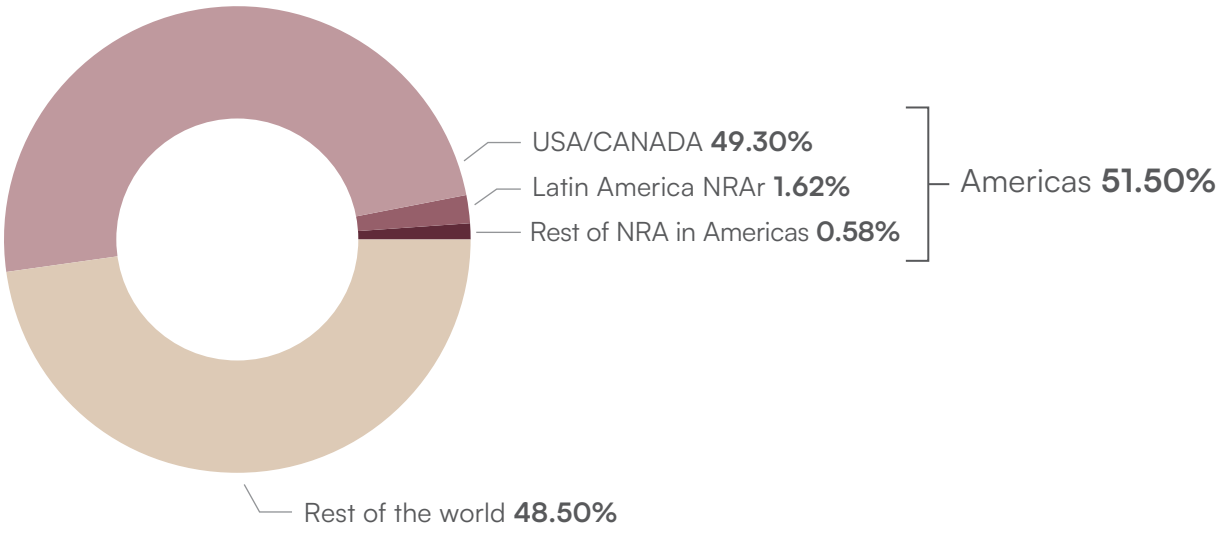
Latin American NRArs use different approaches to PV, including advanced strategies for gathering and assessing ADRs, such as targeted and active surveillance. In addition, some NRArs have established programs to monitor specific medicines on which there are safety concerns (for instance, clozapine and isotretinoin). NRArs also have procedures for systematically collecting and evaluating safety information reports through collaborative projects with public health programs for vaccines, tuberculosis, and malaria.

Between 2015 and 2017, the National Administration of Drugs, Foods, and Medical Devices (Argentina), the Public Health Institute of Chile, and the Colombia National Food and Drug Surveillance Institute took part in a proof-of-concept project as part of a global protocol that used sentinel hospitals to confirm the magnitude of the associations between measles, mumps, and rubella vaccines and idiopathic thrombocytopenic purpura and aseptic meningitis (Bravo-Alcántara et al. 2018).

National ADR reporting

One take-home concept is that the Americas region is responsible for half the reports included in the WHO-PIDM VigiBase. Still, the reports from Latin American NRArs represent only a small share (under 2 percent) (figure 6).

Figure 6 The Distribution of the Reports Included in the WHO-PIDM VigiBase



Source: PAHO 2022.

Despite this small share:

- All NRAr countries exceed the standard population-based reporting ratio of 200.
- On average, 20 percent of all ADR reports to NRArs were serious, although important variations across individual NRArs have been observed.

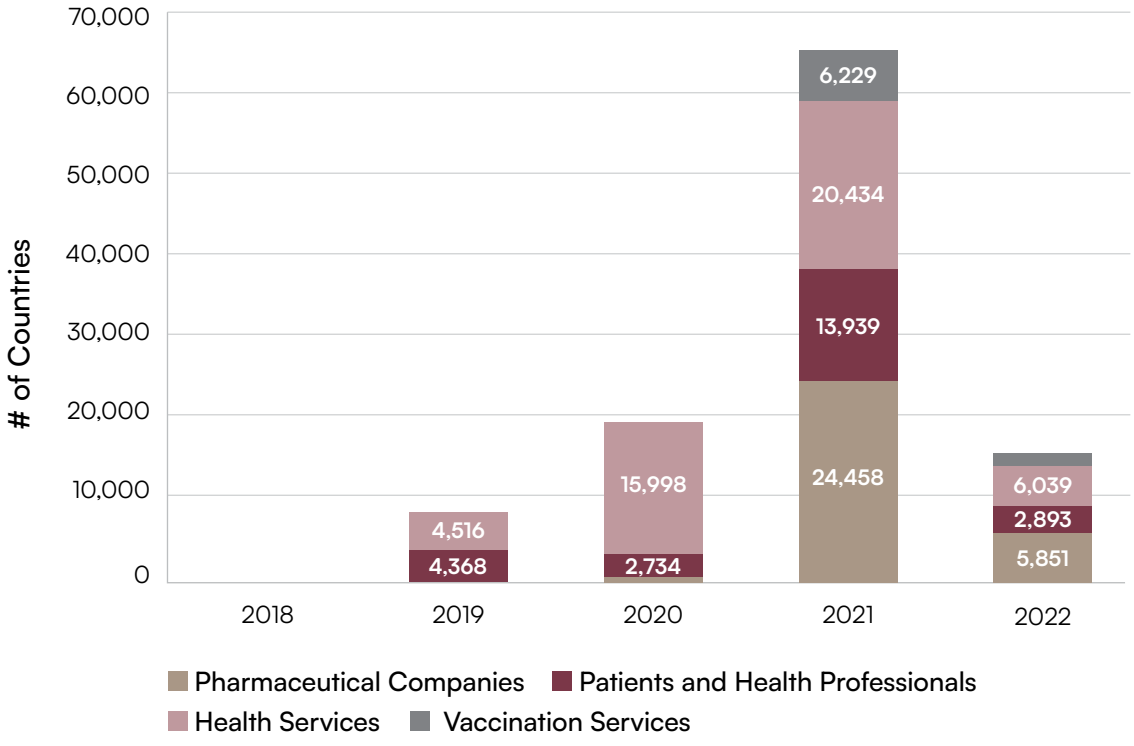
ADR reporting to the NRAs is generally regarded as an indicator of a PV system's development. Higher reporting rates are thought to reflect significantly higher awareness and participation by all stakeholders in a system, including patients, health care providers, marketing authorization holders, and government bodies.

Nonetheless, some NRArs did not submit any reports in 2019, which indicates that many NRArs have no mechanism to ensure continued reporting to VigiBase (PAHO 2022). An important reason behind the differences in reporting is a lack of compatibility between national software and VigiBase. The only way to upload the reports is by manually entering data to VigiFlow, the case report management system developed by UMC to ensure that data are stored, processed, and shared in a standard format. For example, in 2018, the Brazilian Health Regulatory Agency introduced a new software, VigiMed, that is fully compatible with VigiBase. As a result, it has strengthened its capacity for global ADR reporting, and the total number of ADR reports shared with UMC rose from 1,752 in 2017 to more than 25,000 in 2019 (figure 7).

There is, however, no substitute for PV and postmarketing surveillance in one's market, as there may be unique PV interactions in a local population that cannot be found elsewhere or there may be product failures of locally manufactured products that are not sold in other markets.

So, all NRAs must monitor their markets. The PAHO recommends that even the smallest authorities (such as those in the Caribbean and in Central America, where PV systems are the most limited) prioritize PV

Figure 7 Annual PV Reports, Brazilian Health Regulatory Agency



Source: Anvisa 2021.

and postmarketing surveillance and use tools and initiatives, such as the PIDM and the WHO Global Surveillance and Monitoring System, to bolster their approaches (Preston et al. 2020).

Recommendations for action

As a result of this experience, the PAHO report includes the following set of recommendations for action (Preston et al. 2020):

- *Increase stability and allocate appropriate resources* (for example, funding, staff, training) to PV and postmarketing surveillance to ensure that NRAs respond on time to the growing number and complexity of products entering their health systems.
- Improve ADR and substandard and falsified case management, global reporting, and information for regulatory action. These efforts should include facilitating and improving reporting to the NRA through public, provider, industry, and other stakeholder networks. It is also important to maintain dedicated staff who can be assigned to the following:
  - Analyzing and processing reports
  - Sharing and searching regional, global, or other relevant databases
  - Conducting specialized assessments to consider the need for regulatory action
  - Communicating relevant findings to the public
- *Strengthen efforts to tackle illegal online sales* by addressing existing gaps in regulation, by training, and by dedicating regulatory staff permanently to monitor high-risk websites and social media, establish links with law enforcement authorities, and create awareness among users.
- *Establish national track and trace systems in NRAs* to contribute to international monitoring systems and support drug safety–related actions concerning substandard and falsified quality reports.
- *Boost efficiencies in conducting PV and postmarketing surveillance.* This can be done by enhancing information sharing with other NRAs, adopting risk-based postmarketing surveillance strategies, and the ongoing, well-structured monitoring of trusted PV and postmarketing surveillance information sources.

3. Take-Home Messages

3.1. The need for and advantages of a national PV system

- A well organized and structured safety surveillance system for medicines and vaccines at the national level is an asset in helping ensure the quality of health care through the identification of safety alerts and by contributing to the prevention of well-known risks associated with the use of therapeutic procedures and products.
- Genetic, epidemiological, and environmental differences contribute to the heterogeneous response to the medicines and vaccines across the world originating safety problems . It is therefore important that pharmacovigilance systems be developed in all countries and, if possible, cover all geographic areas within countries.
- The safety of any single medicine is never completely known while the medicine continues to be prescribed and used. A strong, wide, and collaborative PV network is the best way to identify new risks and more accurately describe and monitor issues that have already been identified.
- PV systems contribute to build resilience in health systems by (1) helping prevent serious adverse reactions to common medicines, (2) reducing the need for additional treatments or prolonged hospitalization or medical leaves, (3) contributing to improving how medicines are used, and (4) detecting substandard products and unexpected shortages in efficacy.
- PV is a long-run monitoring activity that requires the participation of (1)trained health care specialists to run the system; and (2) many other health care professionals to contribute in the identification and reporting of events and adverse drug reactions among patients.

3.2. The difficulties in consolidating national PV systems

- As discussed in the previous sections of this report, most situation analyses of national PV systems concur in highlighting the lack of continuity in financial support as the commonest problem PV systems face. The discontinuity of funding increases the risk of a high turnover among trained and experienced staff in PV centers, undermining the safety monitoring activities and hindering the development and consolidation of the PV systems.
- Underreporting is a global problem in PV systems. The dissemination of the activities of the PV system, the advantages of reporting, and how to do it could therefore help improve the work performance of the national PV centers. Specific training focused on signal detection and the dissemination of PV results to health care professionals and the population contribute to the development of the PV system.

3.3. Wide collaboration to harmonize actions, share costs, and raise awareness

- A mature PV system is based on three main pillars: appropriate regulation, well-trained, experienced staff, and reports sent by mindful and informed health professionals and citizens. Wide collaboration to harmonize actions, share costs, and raise awareness can help address the limitations faced by different countries, particularly low-and middle-income countries, in these areas.
- Indeed, intercountry and regional collaboration can help meet some of the identified needs in countries, for example, training and technical support from neighboring countries, sharing expertise in the evaluation of reports, and intensifying locally detected signals. Strategies to share costs may represent a solution in the provision of access to international PV experts, designing dissemination campaigns, conducting PV research, and publishing meaningful results. designing dissemination campaigns, conducting PV research, and publishing meaningful results.

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