

THE WORLD MEDICINES SITUATION 2011

PHARMACOVIGILANCE AND SAFETY OF MEDICINES

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SUMMARY

- Pharmacovigilance (PV) aims to improve patient safety through the detection, assessment, understanding and prevention of adverse effects and other drug related problems
- PV, as a discipline, has seen tremendous growth over the past decade, but in response to different needs and priorities worldwide. While 'high-burden diseases' have been the focus in some settings, elsewhere this growth has been driven by a demand for transparency and access to information.
- Recent years have seen a trend towards Good Pharmacovigilance Practice (GPP), particularly in industrialized countries to assure standards and innovations in the collection, management, analysis and use of medicine safety information – with patient safety as the ultimate objective.
- Many resource-limited countries will require additional support (technical and financial) to build PV capacity to effective levels.
- Despite 40 years of PV, patients worldwide continue to be affected by preventable harm from medicines. It is important to analyse and learn from these events.
- For PV to be effective there is a need for timely and responsible communication of the available evidence, involving all stakeholders.
- Many new PV initiatives are being undertaken. But it is important that these efforts are not duplicated and that scarce resources are used wisely.

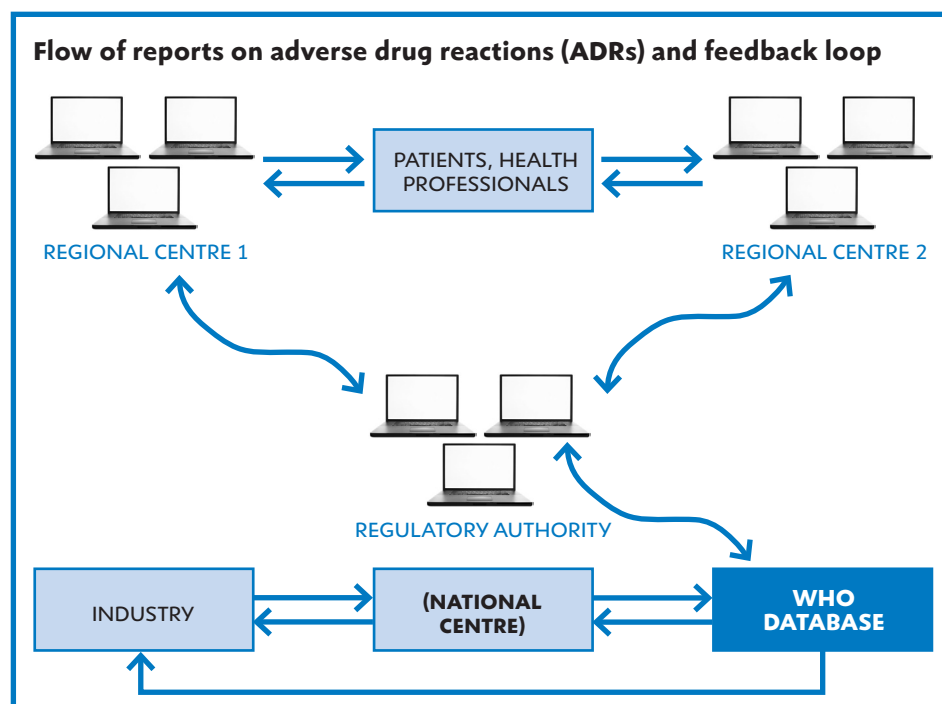
1.1

BACKGROUND/INTRODUCTION

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines (1). It is relevant for anyone whose life is touched in any way by medicines. The thalidomide disaster, detected in 1961, initiated the first systematic international efforts to address medicine safety issues at the global level. The Sixteenth World Health Assembly (1963) adopted a resolution (WHA 16.36) that reaffirmed the need for early action in regard to rapid dissemination of information on adverse reactions due to medicines and subsequently led to the creation of the WHO Pilot Research Project for International Drug Monitoring in 1968. The purpose of this was to develop a system, applicable internationally, for detecting previously unknown or poorly understood adverse effects of medicines. The pilot project has later developed into the WHO Programme for International Drug Monitoring. Under this Programme, systems have been developed in Member States for the collection of individual case safety reports (ICSRs) and their evaluation. Health professionals on observing adverse events report these to a regional or national PV centre. The national PV centre (which is usually a part of or closely linked to the national drug regulatory authority (NDRA)) forwards the reports to a central database that is managed and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in Sweden. Figure 1.1 describes this flow of reports on adverse drug reactions (ADRs) from countries to the UMC). In December 2010, there were 136 countries participating in the Programme. The work of the UMC, with policy directives from WHO, serves the important function of contributing to the work of the NDRA's and other relevant stakeholders, by improving the knowledge of safety profiles of medicines.

This chapter traces the growth of PV over the past 40 years. It highlights gaps in PV at national and international levels, identifies trends and the most urgent PV priorities in defined settings, and sets out the broad elements of a PV strategy designed to promote quality health care and assure patient safety.

FIGURE 1.1



1.2 CURRENT SITUATION

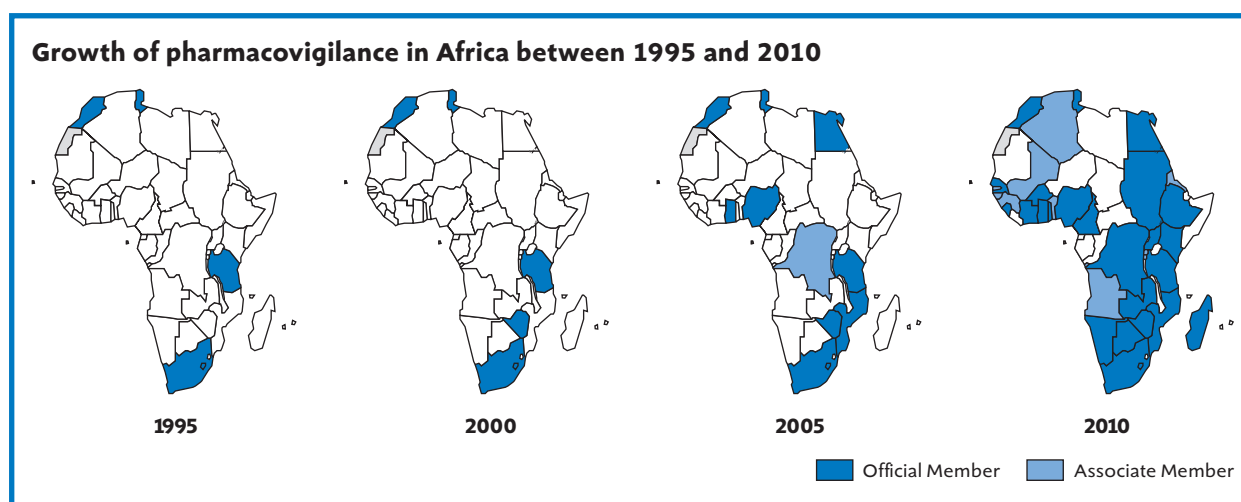
PV has seen tremendous growth over the past 10 years. In Africa, for example, the number of countries with 'good' PV capacity increased from 5 in 2000 to 23 by the end of 2010 (Figure 1.2a, countries in blue). However, the global increase in capacity for PV (Figure 1.2b) has developed for different reasons, to meet different needs, in different parts of the world. While resource constraints and disease demographics, particularly the focus on HIV/AIDS, malaria and tuberculosis, have influenced the growth of PV in developing countries, demand for greater transparency, accountability and access to information has driven PV in the developed world.

Global overview

The actual number of individuals experiencing an adverse reaction is difficult to determine because of low and irregular reporting.

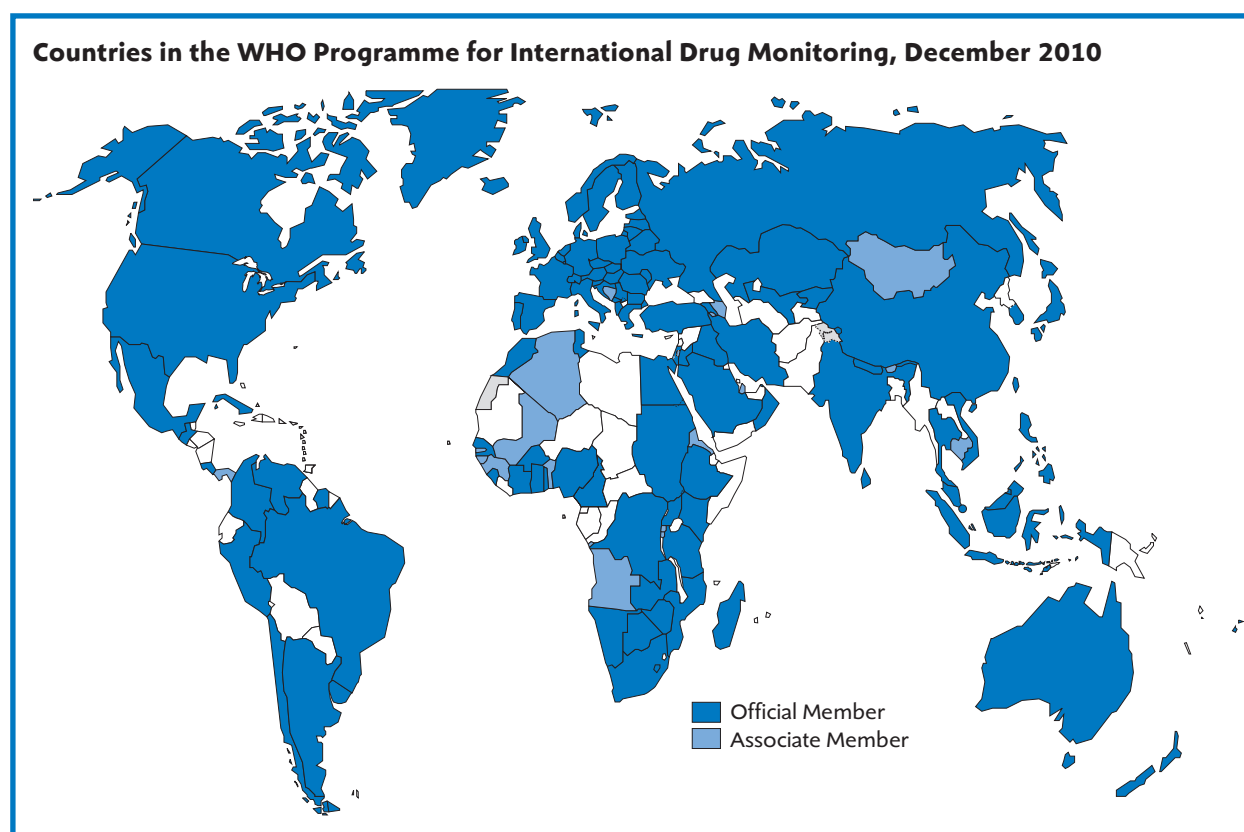
In both developing and developed countries, national PV systems rely heavily on spontaneous reporting systems in which ADRs are reported to an authority by health professionals, manufacturers or directly by patients. Spontaneous reporting systems are the easiest to establish and the cheapest to run and have proven their value in identifying products that need to be recalled from the market (2) and in the early identification of problems (such as the risk of rhabdomyolysis with the statins) that may lead to warnings that something may be amiss (hypothesis generation) (3). However, because of low and irregular reporting, it is difficult to determine the actual number of individuals experiencing an adverse reaction to the medicine. As a result of this uncertainty and lack of information on the number of patients exposed to the medicine in question, it is not possible to estimate rates and frequencies of ADRs through spontaneous reporting. Methods of greater scientific rigour are needed to establish quantitative aspects of medicine safety, to identify specific risk factors and high-risk groups, and to provide valid clinical characteristics of problems associated with specific medicines, both in resource-limited and in well-funded settings.

FIGURE 1.2a



Source: WHO Collaborating Centre for International Drug Monitoring (UMC) (4).

FIGURE 1.2b

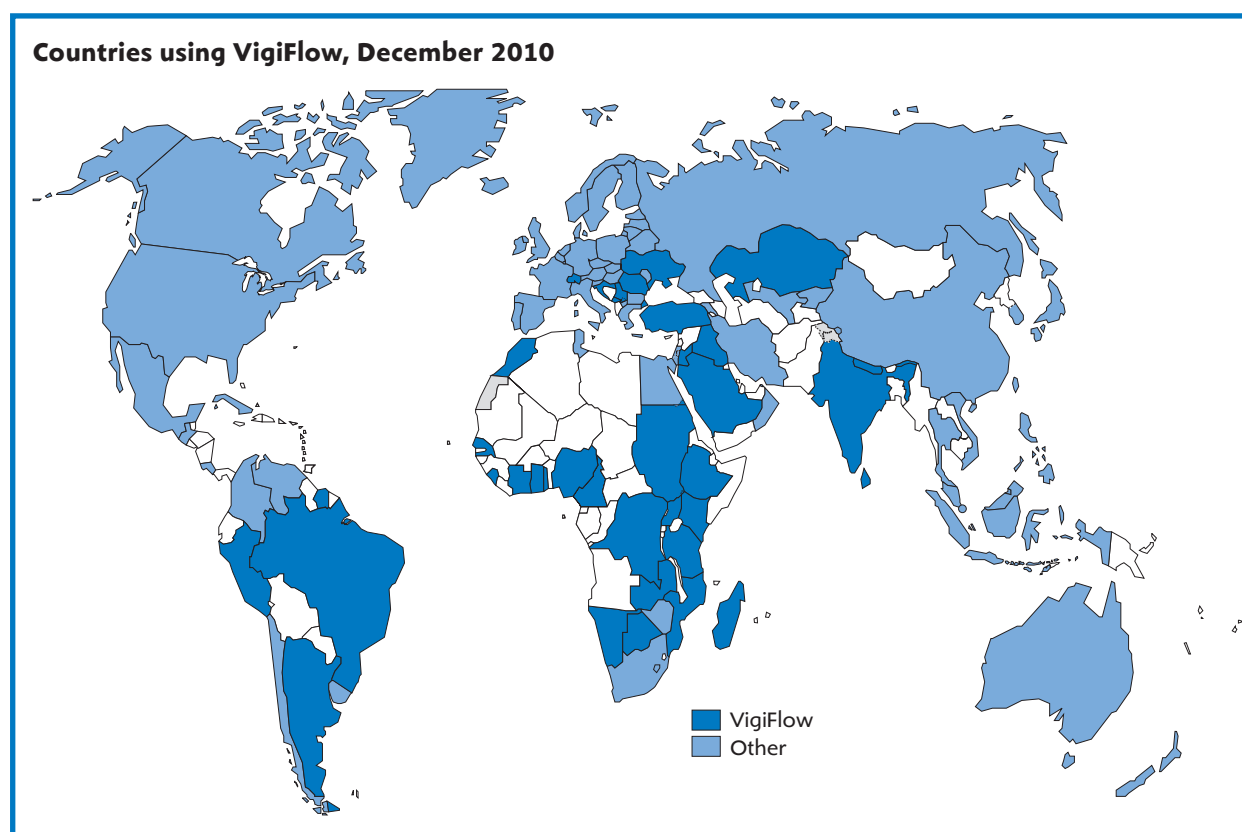


Norms and standards for pharmacovigilance

Systems are in place to develop and promote the use of global norms and standards (5). While harmonized definitions and terminologies for PV exist (6), additional work is needed to define a broader framework for gathering comparable data, as well as data management systems that facilitate data sharing and usage – not only by clinicians but by *all* stakeholders in PV.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (7) is a joint initiative involving both regulators and research-based industry representatives of the European Union (EU), Japan and the USA. This harmonization initiative was established in 1990 to help ICH countries move towards the development of a single, seamless market for pharmaceuticals in their region. ICH has developed over 50 harmonized guidelines to assess and ensure the safety, quality and efficacy of medicines. With current trends in global trade and an open market for pharmaceuticals, the ICH standards are becoming global standards that non-ICH countries are also obliged to comply with. A typical example is seen in the development of the WHO ICSR database over the past decade. According to the ICH standards, ICSR databases have to be 'E2B compatible' (i.e. in a compatible format for the electronic transfer of data). As a result, non-ICH countries are requested to 'upgrade' to these standards in order to be fully compatible with the WHO database. In view of this, and to support countries that do not have a data management system of their own, the UMC has developed a data management tool, *VigiFlow™*, which allows a seamless online submission of ICSRs that include all E2B fields. The tool also allows national centres to manage their data locally, thereby obviating the need for additional software for national database management. At the end of 2010

FIGURE 1.3



VigiFlow was being used by 41 countries worldwide (see Figure 1.3). These developments, together with the emphasis on global cooperation, underscore the important role of an inter-governmental organization such as WHO in safeguarding the interest of resource-limited countries in disseminating information and in providing input beyond the ICH regions.

Highlights of pharmacovigilance in the developed world

Developed countries have more established data processing networks, management systems, databases, and regulatory oversights for systematic follow up of product safety.

In Europe, the most significant PV development has been the introduction of EudraVigilance, a data processing network and management system for reporting and evaluating suspected ADRs during the development of and following the marketing authorization of medicinal products in the European Economic Area (EEA) (8). This includes a European PV database and is expected to support European regional PV and regulatory needs. In addition, the European Union recently initiated the European Network of Centres for Pharmacoeconomics and Pharmacovigilance (ENCePP) (9) intended to further strengthen the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre *independent post-authorization safety studies* and studies focusing on lack of efficacy.

Several developed countries already maintain patient record databases and provide services that are suitable for outcome research. Examples are the General Practice Research Database (GPRD) (10) and the Prescription Event Monitoring (PEM) (11) scheme in the United Kingdom, and the Medicaid databases in the USA (12). An additional development has been the inclusion of patients as reporting partners in the PV networks in Australia, Canada, the USA, and in some countries in Europe (e.g. Denmark, the Netherlands, Sweden and the United Kingdom).

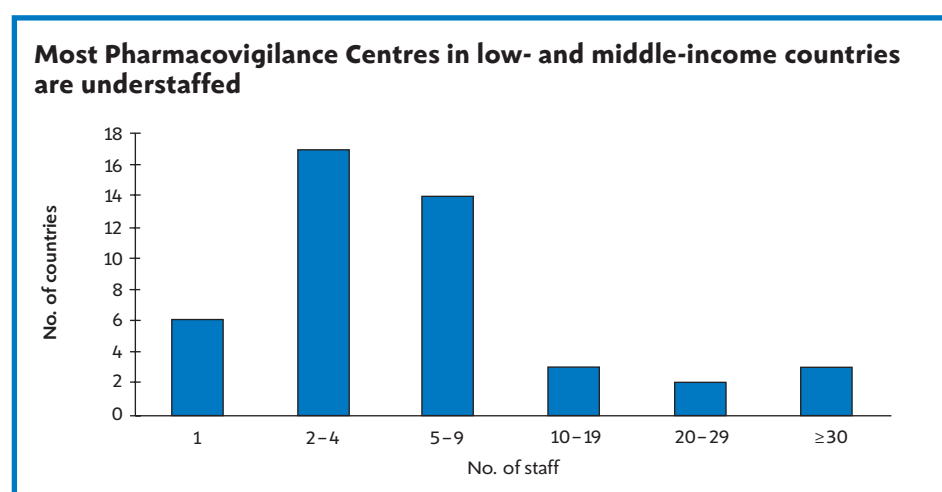
In developed countries, regulatory systems exist for regular and systematic follow-up of product safety. Product sponsors are required to submit Periodic Safety Update Reports to the relevant NDRA (13). In November 2004, the ICH published a new guideline, E2E: Pharmacovigilance Planning. This is intended to provide guidance for planning PV activities, especially in preparation for the early post-marketing period of a new drug. The guideline has been adapted for use in Europe and the USA, and pharmaceutical manufacturers in these countries are now required to provide Risk Management Plans (RMPs) for new medicines in connection with the submission of an application for marketing authorization. The pharmaceutical industry is also encouraged to engage in active PV methods and epidemiological studies, to complement spontaneous reporting. The use of pregnancy registries has increased in recent years as an active method of detecting outcomes of pregnancies in women who have been inadvertently or deliberately exposed to pharmaceuticals during pregnancy. This has been encouraged by the NDRAs as part of the post-authorization monitoring of medicines (14).

Pharmacovigilance in the developing world

A recent assessment of PV in 55 low- and middle-income countries highlighted important characteristics and gaps in these settings (15). In general, most of the PV centres in developing countries were established after 1990, and most centres are severely understaffed (Figure 1.4) and under-resourced. Recently the PV agenda in these settings has become very much donor-driven, with most efforts going into setting up PV programmes for medicines used in public health programmes, typically for malaria and HIV (Figure 1.5). However, most centres are also involved in other activities such as medicines information, promoting patient safety and rational use of medicines, and in providing information on poisons. Spontaneous reporting is the rule, but there is now interest in the introduction of active surveillance of cohorts of patients in specific disease programmes, as with Cohort Event Monitoring (CEM) (16). Two such programmes supported by WHO are already under way for artemisinin combination therapies (ACTs) in Nigeria (see Box 1.1) and the United Republic of Tanzania (17). Some countries have also established pregnancy exposure registries and sentinel sites that serve to monitor special populations (HIV/AIDS patients, children). The WHO Special Programme for Research and Training in Tropical Diseases (TDR) has

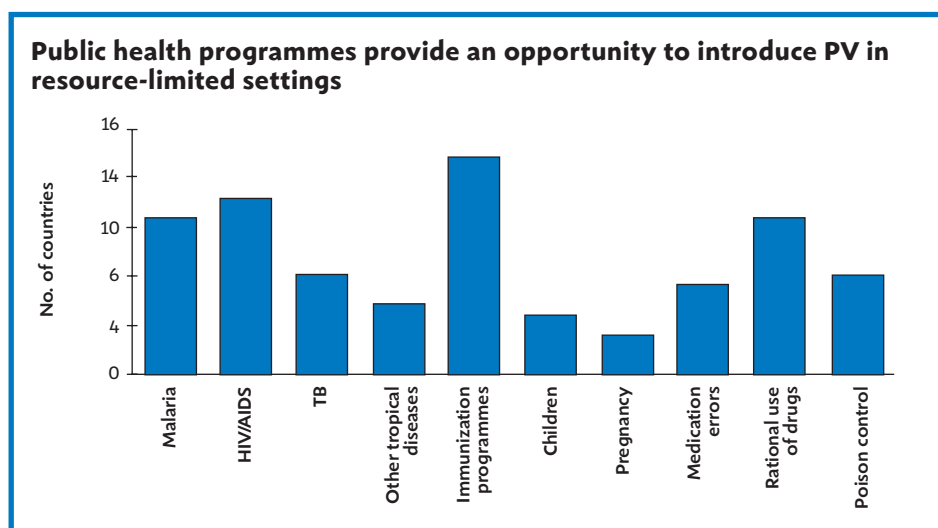
Growth of PV in low- and middle-income countries has been influenced by a disease focus on HIV/AIDS, malaria, tuberculosis and health programmes on children and mothers.

FIGURE 1.4



Source: An analysis of pharmacovigilance activities in 55 low- and middle-income countries, Olsson et al, *Drug Safety*, 2010; 33(8): 689–703 (15). (With permission from Adis, a Wolters Kluwer business (©) Adis Data Information BV [2010]. All rights reserved.)

FIGURE 1.5



Source: An analysis of pharmacovigilance activities in 55 low- and middle-income countries, Olsson et al, *Drug Safety*, 2010; 33(8): 689–703 (15). (With permission from Adis, a Wolters Kluwer business (©) Adis Data Information BV [2010]. All rights reserved.)

developed a protocol for setting up registries to monitor the outcomes of pregnancies following early exposure to treatment with pharmaceuticals (e.g. for malaria or HIV/AIDS) in resource-limited settings (18). WHO (TDR and the Department of Making Pregnancy Safer) is assessing the feasibility of setting up pregnancy registries in Africa. However, a major difficulty in these settings is the lack of background data on pregnancy outcomes in a normal or unexposed population. In Zambia, a key resource for this is the Zambian Electronic Perinatal Record System (ZEPRS), a population-based pregnancy registry recording 45 000 deliveries a year at the University Teaching Hospital in Lusaka (19). This system aims to provide basic data on birth weights, birth measurements and general aspects of pregnancy outcomes via electronic records. By including the pregnant population in Zambia, the effects on pregnancy outcomes of ‘external’ influences, including medicines, can be compared against the background occurrence of those effects in the Zambian population. Most of these initiatives are new and their usefulness and impact on PV locally and globally are yet to be ascertained.

BOX 1.1

Active surveillance of patients on antimalarial medicines in Nigeria

- The Cohort Event Monitoring Programme (CEM) in Nigeria was set up to monitor patients on artemether-lumefantrine (AL) and artesunate-amodiaquine (AA).
- When completed, CEM will help characterize rates, risk factors and frequencies of adverse events in these patients, and help determine whether medicines are being prescribed rationally.
- A cohort of 2936 (out of 3010 patients treated with either AA or AL) has been followed up so far. A larger cohort (about 10 000 patients) is needed for higher statistical power.
- There is general enthusiasm for this type of surveillance among health professionals, although it is considered as being resource-intensive and with the risk of ‘loss to follow-up’ of treated patients.

Source: Report of the 32nd Annual Meeting of Representatives of National Centres participating in the WHO Programme for International Drug Monitoring, Rabat, Morocco, 2009.

1.3

TRENDS OVER THE PAST 5–10 YEARS

Drug withdrawals and lessons learnt

Current issues of concern in drug withdrawals include adequacy of PV methods, capability of the regulatory systems, collection and use of evidence, communication of decisions, transparency and information sharing.

Recent market withdrawals of medicines with high market penetration (e.g. cerivastatin (20) and rofecoxib (21)), uncertainty about the safety of antidepressants in children and adolescents (22), and the confusion over reports of cardiac events associated with rosiglitazone (23) have intensified questioning about safety issues, both within professional circles and in civil society. Key issues of concern include: the adequacy of current PV methods and the appropriateness of current regulatory systems; the role of regulators, industry and academia in collecting evidence; use of evidence in decision-making; communication of decisions; and, above all, the need for transparency and information sharing. Some regulators have responded to these debates by setting up systems of greater transparency. Providing early public communication of any ongoing safety reviews (24) is one such response. The pharmaceutical industry is required by stringent regulatory agencies to provide full details of risk management plans prior to product approval, with clear PV plans that identify risk, characterize and/or quantify risks and delineate risk minimization activities for the product (25). But these efforts have so far been restricted to the developed world. Nothing has yet been done to adapt these measures in order to ensure patient safety in the developing world. This is a serious gap that needs to be addressed.

Pharmacovigilance for high-burden diseases

Fast-track approvals and rapid scale-up of access to new medicines for which little post-marketing experience exists have added to the vulnerability of developing countries in dealing with medicine-related adverse events.

In the developing world, malaria, HIV/AIDS, tuberculosis and immunization programmes have received a lot of attention as part of the initiatives to achieve the Millennium Development Goals. The Prequalification of Medicines Programme (PQ) (26) and the availability of assured quality generic medicines have dramatically reduced the cost of treatment for these diseases in resource-limited countries. However, these efforts have fallen short in not including plans for any PV component or measures for strengthening regulatory systems. Fast-track approvals and rapid scale-up of access to new medicines with little post-marketing experience have added to the vulnerability of these countries and their inadequacies in dealing with medicine-related emergencies (as with amodiaquine-artesunate combination preparations) (27,28,29,30).

Between 2003 and 2008, access to antiretroviral medicines (ARVs) in low- and middle-income countries rose ten-fold (31). In caring for HIV patients, short- and long-term toxicity data have a critical role in informing treatment choices and decisions around when to substitute or switch drug regimens. Yet very little information is available on ADRs in these settings. The majority of known data on ADRs are derived from cohort studies or clinical trials conducted in North America, Europe and Australia, and based on innovator drug products. It is vital to gather data on ADRs in resource-limited settings, since different populations with different co-morbidities are being treated compared to those in resource-rich countries. These data are essential to inform policy and country or regional treatment guidelines, to provide better information for patient management (32). In recent years there have been more concerted efforts by WHO and other stakeholders to address some of these gaps. In some countries in sub-Saharan Africa, for example, efforts are under way to introduce the principles of active surveillance for the prospective follow-up of patients on HIV treatment, to better characterize the toxicity profile of ARVs in this population (33). Efforts to address the PV needs in the treatment of specific diseases have provided an opportunity to introduce PV systems into PV-naïve countries (34) in this region. As a result, the number of countries in sub-Saharan Africa with functional PV centres has increased substantially

in recent years, from under 10 in 2000 to well over 20 countries by 2010 (Figures 1.2a and 1.2b).

In addition, the components of a Risk Management Plan are being implemented, for at least some products, through PQ. Meanwhile, global health initiatives such as the Global Fund to Fight AIDS Tuberculosis and Malaria (GFATM), the Bill and Melinda Gates Foundation (BMGF) and UNITAID (the International Drug Purchase Facility) are also expressing interest in supporting projects to monitor the safety of medicines that are being brought to the countries through these initiatives. However, these projects will again be limited in their objectives and will not necessarily contribute to building long-term PV systems unless there is a conscious decision to cooperate and align with country needs (35,36).

Bringing in other stakeholders

Patients and consumers need to be involved in PV networks.

One of the reasons why pharmacovigilance systems are not fully functional and effective is that many stakeholder groups do not participate sufficiently in the reporting of ADRs. In most countries, only health professionals are currently encouraged to report ADRs. Yet it has been demonstrated repeatedly that health professionals only forward a small minority of all reports (37,38). Increasingly, therefore, more attention is being given to the collection, recording and analysis of ADRs reported by other stakeholders, including patients and consumer organizations.

Worldwide, some efforts are being made – for example, in Australia, Canada, Denmark, the Netherlands, the Philippines, Sweden, the United Kingdom and the USA – to include consumer organizations in the national PV network. Early results of these efforts indicate that new dimensions of drug-related problems can be identified and described sooner by patients themselves (39,40).

However, if consumer reporting is to be optimized, methodology and best practice must be internationally agreed upon and promoted, so that consumer reporting is harmonized and comparative analysis made possible. Supported by the EU, WHO and the UMC are engaged in a project that aims to strengthen consumer reporting of ADRs through review of existing consumer reporting methods, identification of optimal methods, and training in best practice in consumer reporting of medication-related problems (41).

Pharmacovigilance and patient safety

The ultimate aim of PV is to improve patient safety. While knowledge of appropriate and safe use of medicines has grown over the years, there remains a considerable gap between knowledge and action. A deeper understanding is needed of factors causing preventable ADRs, to develop methods to mitigate or avoid them, and to evaluate the effectiveness of drug safety efforts aimed at improving patient safety. This involves working with all stakeholders, including the World Alliance for Patient Safety which was established in response to World Health Assembly Resolution 55.18 (42). The UMC has been collaborating with the Alliance on its work related to reporting and learning systems for patient safety (43).

Studies of adverse events in developed countries have consistently shown that safety issues related to the use of medicines are one of the leading causes of preventable harm to patients. But in recent years these issues are being debated also in the developing world (44). A joint project involving WHO and the Moroccan National Pharmacovigilance Centre investigated the possibility of an extended role for PV centres, to capture information on adverse events related to medication errors. A retrospective analysis of ICSRs in the Moroccan database

identified the groups of medications 'most involved' in preventable adverse events (see Table 1.1). The medication errors associated with these preventable adverse events occurred most often at the prescribing and administration stages (45). Capturing comprehensive data (what, how and why) as a source of learning is the basis for identifying areas of change, recommendations and sustainable solutions for minimizing the recurrence of the incident (46). The pilot project is thus an important first step aimed at deepening our understanding of systemic failures responsible for the adverse events relating to drug prescribing, dispensing and administration.

TABLE 1.1 Medication classes most involved in preventable adverse drug events in Morocco

Medication class	Percentage
Antibacterials for systemic use	20.6
Analgesics	12.8
Psycholeptics	11.8
Anti-inflammatory and anti-rheumatic products	11.2
Propulsives	5.9

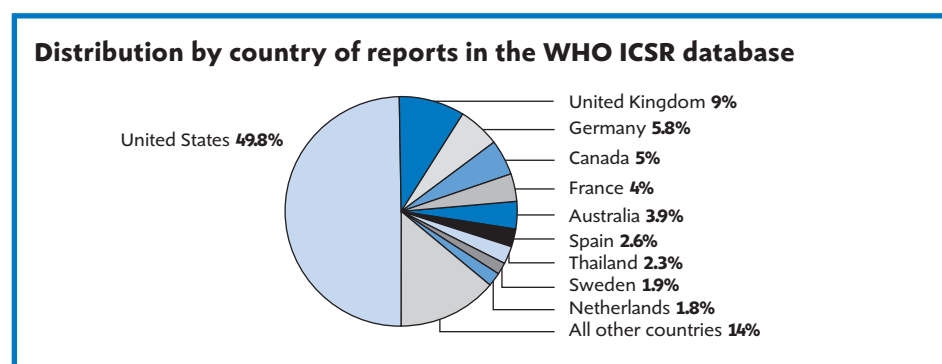
Source: Detecting medication errors in pharmacovigilance database: capacities and limits. Alj L et al., 2007, *International Journal of Risk and Safety in Medicine* (45). (With permission from IOS Press, Amsterdam).

The WHO global ICSR database

The WHO global ICSR database is situated in the UMC in Sweden. As of December 2010, it contained 5.8 million ICSRs from the 104 full participating members of the WHO Programme for International Drug Monitoring (see Figure 1.6 for distribution of reports by country).

The data are sent by the national PV centres and are regarded as their property, held in trust by WHO. In many cases, the reports submitted to the UMC describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most cases, it cannot be established whether a pharmaceutical product or ingredient is the cause of an event. The reports, which are submitted to national PV centres, come from both regulatory and voluntary sources. Some national centres accept reports from medical practitioners only; others accept reports from a wider spectrum of health professionals; and some centres include reports received from pharmaceutical companies and directly from patients in the information submitted to the Collaborating Centre (see Figure 1.1). The volume of reports for a particular pharmaceutical product may be influenced by the extent of use of

FIGURE 1.6



Source: UMC, December 2010.

the product, publicity and the nature of the reactions, as well as other factors which may vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to a particular product. Data can be misinterpreted by those not familiar with these limitations; therefore only national centres have access to the WHO database. However, other stakeholders with a legitimate interest in PV data can request a search of the database.

Signal detection

The primary function of PV is to provide early warnings ('Signals') of hitherto unknown ADRs. The sources of these Signals include spontaneous reporting systems, prescription event monitoring, case controlled surveillance, record linkages, clinical trials databases and registries. Recent additions to these sources include large comprehensive population databases, such as electronic health-care records, health insurance systems and IMS Health, the world's largest aggregator of prescription data.

Since 1998, an advanced signalling process that uses Bayesian logic (Bayesian Confidence Propagation Neural Network, BCPNN) has been an important development in the data mining of the large amount of information in the WHO ICSR database. The BCPNN and other statistical methods have a high 'early' predictive value and can greatly enhance the traditional signal detection procedures. The methods are useful in detecting both specific drug-adverse reaction signals for individual drugs and in examining complex dependencies in the data set (e.g. one event caused by the interaction of several drugs). However, the usefulness of these methods relies on the amount and quality of the data available (47,48). These methods, therefore, must always be complemented by a clinical review process.

Substantiation of evidence

Spontaneous reporting systems and ICSRs were the mainstay of PV in the early 1960s, in view of the need for early detection of serious and unexpected effects of new drugs at the time. But it is important to consider that spontaneous reporting has been designed as a system for 'hypothesis' generation. Further study, using other methods, are needed to test the hypothesis (49). Additionally, from an epidemiological aspect, ICSRs are sometimes considered insufficient to prove a relationship between a drug and an adverse event. Drawbacks include reporter bias, drug use factors and the lack of quantification of numerator and denominator. Other data sources besides ICSRs are needed to provide the missing information. In many ICH countries, large health-care databases have been used to perform observational studies. Today in developed countries there is a move towards proactive risk management throughout the lifecycle of a medicine, including substantiation of evidence in terms of quantification of harm, relative risk assessment to yield evidence for appropriate treatment strategies, and identification of risk factors.

In developed countries, there is a move towards proactive risk management throughout the lifecycle of medicines.

Post-authorization safety studies (PASS)

In the current European regulatory system, substantiation of evidence is mainly the responsibility of the holder of the marketing authorization. At the time of approval, proposals for post-authorization safety studies (PASS) to further assess safety concerns should be submitted to regulatory authorities. However, evaluation of the first cohort of RMPs indicated that information in approximately two out of five study proposals for PASS was too limited, precluding an adequate scientific assessment (50).

Non-sponsor studies

Several initiatives such as the ENCePP and the Sentinel Initiative of the US Food and Drug Administration (FDA) indicate a shift towards sponsor-independent studies.

Population databases, registries, international cohorts and data linkages

Biopharmaceuticals, i.e. products where the active substance is produced by or extracted from a biological source, represent a growing part of the therapeutic arsenal. In recent years the EU has approved a number of 'biosimilars' (e.g. somatotropin, epoetin). The primary safety concern with products of this type is immunogenicity (51). Existing large population-based databases, often based on general practitioners and community pharmacy data, include limited data on biopharmaceuticals as these medicines are often used in specialized (hospital) settings or directly delivered to the patient (52). Much better cooperation between all stakeholders is therefore needed to fully understand and address the PV challenges posed by biosimilars (53).

Quality PV data can also be obtained from sources such as disease and exposure registries (see previous section: PV in the developing world). Good examples of pregnancy registers exist in the Nordic countries (54), and there are some well-established registries in the field of rheumatoid arthritis (55). However, potential problems with registries include the willingness of patients and health professionals to participate, and the expense and time involved in setting up a registry.

There is also a move to integrate databases of 'treatments versus events' across countries (e.g. the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study and the International Epidemiological Databases to Evaluate AIDS (IeDEA) databases), case control assessment, drug utilization data, electronic health records, and spontaneous reporting for the substantiation of PV evidence. But as these synergies evolve, new barriers such as privacy issues, medical ethics, governance and data access will inevitably emerge.

Using pharmacovigilance information

Regulatory and policy aspects

Once a safety issue has been identified and validated it must be communicated to the NDRAs for appropriate action. In developed countries, data collected in PV systems are most commonly used for drug regulatory activities such as updating the product information or suspending or withdrawing a product from the market. But this is not the case in many developing countries (Table 1.2), presumably because the information received is considered inadequate to trigger or support regulatory decisions. A majority of these countries share PV information with public health programmes, drug information centres and health professionals/Drug and Therapeutics Committees (DTCs). Pharmacovigilance information is less commonly used as a background when elaborating Essential Medicines Lists, therapeutic guidelines or in providing information to the public.

Patient care and case management

Health professionals need much more support and information than is available in Summaries of Product Characteristics (SPCs) in order to prevent, diagnose and manage the relatively rare ADRs. The information needs to be up-to-date, well-collated, analysed, and validated and presented in a system that is easy to navigate and process. The Cochrane Collaboration

TABLE 1.2 Number of countries carrying out regulatory actions in 2007 on the basis of pharmacovigilance activities in own country

Action taken	No. of countries taking action	No. of times action taken		
		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: An analysis of pharmacovigilance activities in 55 low- and middle-income countries, Olsson S et al., *Drug Safety*, 2010, *Drug Safety*, 2010, 33(8):689–703 (15). (With permission from Adis, a Wolters Kluwer business (©) Adis Data Information BV [2010]. All rights reserved.)

assembles proven clinical trial information on specified areas, but it is not comprehensive, excluding other information such as ICSRs. The National Institute for Health and Clinical Excellence (NICE), UK, and others also provide therapeutic guidance, taking into account efficacy, safety and cost. While these and many other databases are good resources, it is not easy for a busy health professional to readily access all of them when required. The Health on the Net Foundation (www.hon.ch) does provide a useful model for what could be the way forward in giving access to a variety of web sites that meet established standards. The Foundation's web site provides easy access to scientific information (such as MEDLINE) as well as information from meetings and discussion groups. But these web sites would probably be more useful if they included practical advice and answers to frequently asked questions. Overall, it is clear that drug safety issues are rarely put into context alongside issues such as effectiveness (or cost). Although some studies have done so, these require time-consuming searches to access them, via MEDLINE or Google.

Communication in pharmacovigilance

Effective communication is essential in any PV endeavour. Effective communication helps overcome scares related to rumours and half-truths (56), especially in public health programmes, and provides redress and reassurance against poorly communicated scientific facts (57). The Erice Declaration of 1997 (58) and Erice Manifesto of 2006 (59), developed by experts in collaboration with the UMC and other partners, provide guiding principles for effective communication between and among various stakeholders, including 'pharmacovigilantes', regulators, health professionals, academia, the scientific community and the general public. Because PV is a continuous risk-benefit assessment, and because perception of risk will be very different across the different stakeholders, the communication of risk-benefit assessment is a huge challenge that involves presenting understandable, coherent information in a responsible way. The controversies around the withdrawal of rofecoxib (60) and reports of psychosis with SSRIs (61) highlight the current need for effective, timely and transparent sharing of medicine safety information. Regulators and manufacturers have access to raw data in order to perform risk-benefit assessments (62). However, NGOs do not have similar access. The lack of availability of information in pre-marketing dossiers and the existence of unpublished studies have led to distrust among health professionals and consumers, both towards industry and regulators (56,57). In aiming for a more 'informed' global partnership, WHO operates the Information Exchange system (63) for bridging the

information gap between the developed and the developing world. WHO and its Member States will need to work together, and with all the relevant stakeholders, to develop optimum standards and strategies for communicating medicine safety issues.

1.4

FUTURE CHALLENGES AND ISSUES

The role of an international organization such as WHO is essential to coordinate and promote best practices in PV.

Although PV originated in the 1960s and is now firmly established in industrialized countries, it is still a new concept in many low- and middle-income countries. Current interest from global health initiatives (such as GFATM, USAID and BMGF), particularly in public health programmes, are providing opportunities to introduce the basic principles of PV in resource-limited settings. However, these must be appropriately aligned to country needs and capacities if they are to have a long-term impact. For example, before a pharmaceutical industry can be expected to meet its PV obligations, there needs to be a well organized and competent regulatory system in place. Future challenges will include guarding against the creation of parallel systems that duplicate efforts, and of structures that add to the burden of already fragile health systems and waste precious resources or, worse, are so diverse that they make meaningful collation impossible. In this environment the presence of an international organization such as WHO is essential to coordinate and promote best practices in PV.

There is sufficient evidence to suggest that patients and consumers are important partners for PV. There is a need to make information more accessible and available to the public even while protecting the confidentiality of the individual patient. The scope of PV needs to be expanded and the link between PV and patient safety needs to be a lot more tangible – underscoring the fact that current efforts in drug safety monitoring have the ultimate objective of protecting patients from avoidable harm from medicines.

Although traditionally PV centres have focused on ‘capturing’ events related to the intrinsic nature of a medicine, centres are now increasingly capturing all kinds of drug-related problems including: unexpected lack of efficacy; quality defects; drug abuse; medication errors; interactions with traditional and herbal medicines; and poisoning events that are not necessarily related to the intrinsic nature of the medicines. A comprehensive PV strategy for a country will be one that ensures reasonable economies of scope, that is, one that helps build a system that can serve the PV needs of multiple health conditions, a system that can meet a country’s specific needs. It must identify and elaborate feasible systems, governance, infrastructures, human resources, training and capacity building, sustainable methodologies and innovations. A key component of this should be the dissemination of medicines safety information to policy-makers and regulators and knowledge sharing through accessible, quality informatics and learning tools.

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ABBREVIATIONS

AA	Artesunate-amodiaquine
ACT	Artemisinin combination therapies
ADR	Adverse drug reaction
AL	Artemether-lumefantrine
ARVs	Antiretroviral medicines
BCPNN	Bayesian Confidence Propagation Neural Network
CEM	Cohort Event Monitoring
CIOMS	Council for Organizations of Medical Sciences
DAD	Data Collection on Adverse Events of Anti-HIV Drugs
DTC	Drug and Therapeutics Committee
EEA	European Economic Area
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	US Food and Drug Administration
GPP	Good Pharmacovigilance Practice
GPRD	General Practice Research Database
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual case safety report
NDRA	National Drug Regulatory Authority
NICE	National Institute for Health and Clinical Excellence
PASS	Post-authorization safety studies
PEM	Prescription event monitoring
PQ	Prequalification of Medicines Programme
PV	Pharmacovigilance
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
TDR	WHO Special Programme for Research and Training in Tropical Diseases
UMC	Uppsala Monitoring Centre
UNITAID	International Drug Purchase Facility
ZEPRS	Zambian Electronic Perinatal Record System

