ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (8): 689-703
0114-5916/10/0008-0689/$49.95/0

Pharmacovigilance Activities in 55 Low- and Middle-Income Countries

A Questionnaire-Based Analysis

Sten Olsson,[1] *Shanthi N. Pal*,[2] *Andy Stergachis*[3] and *Mary Couper*[2]

1 WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
2 Quality Assurance and Safety of Medicines, World Health Organization, Geneva, Switzerland
3 Departments of Epidemiology and Global Health, School of Public Health, University of Washington, Seattle, Washington, USA

Abstract

Background: The WHO Programme for International Drug Monitoring aims to develop a comprehensive global pharmacovigilance strategy that responds to the healthcare needs of low- and middle-income countries. However, first there is a need to measure and understand existing conditions and pharmacovigilance initiatives intended in these settings. Very few investigations have carried out such a systematic assessment of the pharmacovigilance landscape in recent years in low- and middle-income countries.

Objective: To assess current and planned pharmacovigilance activities in low- and middle-income countries, identify gaps and the most urgent pharmacovigilance priorities at national and international levels, and define the elements of a sustainable global pharmacovigilance strategy.

Methods: A standardized questionnaire was sent to 114 representatives of countries participating in the WHO Programme for International Drug Monitoring (but excluding Australia, Canada, New Zealand, Switzerland and the International Conference on Harmonization countries, i.e. countries in Europe, Japan and the US) and to a few other identified contacts from non-member countries. The questionnaire was sent out between March and July 2008 and was designed to collect information on the structure, resources, functions and achievements of pharmacovigilance systems in low- and middle-income countries, with a focus on pharmacovigilance activities supported by national health authorities including public health programmes. All questionnaires that were returned by the end of July 2008 were used in the analysis.

Results: Fifty-five completed questionnaires were received by July 2008, representing a response rate of 55.5%. Forty-five percent of the pharmacovigilance centres in the analysis were established during the 1990s and 49% were set up later; 69% were affiliated with their Drug Regulatory Agency, 20% with the Ministry of Health and 9% with a university or other scientific body. Few countries (23 of 55) have any budget allocated for pharmacovigilance.

Public health programmes (44%), the Global Fund to fight AIDS, Tuberculosis and Malaria (36%), universities (26%), poison centres (21%), Management Sciences for Health (18%) and Rational Use of Drugs networks (15%) sponsor some pharmacovigilance activities. In addition to direct pharmacovigilance activities, many centres are also involved in other activities such as drug information (63%), promoting patient safety (52%), rational use of drugs (46%) and poison information (15%). Some countries have sentinel sites to monitor HIV/AIDS patients (in seven countries) and other special groups. Information gathered through pharmacovigilance activities is used to assist regulatory functions in most countries (n = 42), lack of training and funding were mentioned as being major challenges to pharmacovigilance in many countries.

Conclusions: This study has helped identify some of the special challenges and barriers to promoting pharmacovigilance in low- and middle-income countries. A pharmacovigilance strategy in these settings needs to help build health systems that can serve the purpose of multiple health conditions. It needs to identify and implement feasible systems, governance, infrastructures, human resource, training and capacity building, sustainable methodologies and innovations in pharmacovigilance; a key component will be the dissemination of medicines safety information to policy makers and regulators and knowledge sharing with healthcare professionals through high quality informatics and learning tools, with rational use of medicines and patient safety as the ultimate goal of pharmacovigilance.

Background

The scale-up of treatment programmes in regions with high disease burdens and co-morbidities offers a unique opportunity to establish and test frameworks for systematically capturing, evaluating and reacting to pharmacovigilance information obtained in these challenging settings. However, efforts to improve access to medicines used in resource-limited settings have not included a proportionate development in pharmacovigilance practices in these countries, partly because of the numerous challenges in monitoring the safety of medicines, including:

- use of newer medicines for which there is only limited experience from pre-marketing clinical trials and limited knowledge of use;
- overburdened healthcare systems, poor drug control/legislation, informal drug markets (at which counterfeit and sub-standard pharmaceuticals are often sold);
- poor record keeping of medication exposures and outcomes, including recording of any adverse events;
- significant resource constraints.

The WHO Programme for International Drug Monitoring (hereafter referred to as the WHO Pharmacovigilance Programme) aims to address these challenges through a comprehensive global pharmacovigilance strategy that responds to the needs of low- and middle-income countries while taking into account the state-of-the-art and intended pharmacovigilance initiatives in these countries. Ten years ago the WHO Collaborating Centre for International Drug Monitoring, known as the Uppsala Monitoring Centre (the UMC) carried out a systematic analysis of national pharmacovigilance systems worldwide.[1] Few studies have been carried out since, to document the current-day pharmacovigilance problems and characteristics, particularly in low- and middle-income countries in multiple regions

around the world. Some efforts refer to the pharmacovigilance situation in countries only as a secondary analysis, for example, of regulatory capacity or spontaneous reporting methods in countries.[2-4]

In 2008, the WHO Pharmacovigilance Programme, the UMC and the University of Washington carried out a baseline investigation to document the existing pharmacovigilance situation in low- and middle-income countries. The investigation aimed to assess current and planned pharmacovigilance activities in a global setting, identify gaps in pharmacovigilance at national and international levels, determine the most urgent pharmacovigilance priorities in defined settings and define the elements of a sustainable global pharmacovigilance strategy.

This article presents the pharmacovigilance situation in 55 countries and provides important baseline information that can be regarded as representing current practices and gaps in low- and middle-income countries from around the world. The information collected will help identify the most urgent pharmacovigilance priorities and the way forward.

Methods

A survey of the pharmacovigilance system in 55 countries was carried out between March and July 2008. A standardized questionnaire (see Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A30) was developed in English and translated into French and Spanish. The questionnaire was sent to 99 representatives of countries participating in the WHO Pharmacovigilance Programme; it was also sent to contacts identified from non-member countries. Since the survey was designed to study the pharmacovigilance situation only in low- and middle-income countries, the questionnaire was not sent to any contacts in the International Conference on Harmonization (ICH) countries (i.e. EU, Japan and the US) or to contacts in Australia, Canada, New Zealand or Switzerland. The questionnaire was designed to collect information on the structure, resources, functions and achievements of pharmacovigilance systems in low- and middle-income countries. The focus of the questionnaire was on pharmacovigilance activities supported by national health authorities including public health programmes. It referred to eight broad areas:

- an overview of the pharmacovigilance programme;
- pharmacovigilance activities;
- spontaneous reporting;
- sentinel sites and active surveillance;
- registries;
- use of information;
- challenges and future activities;
- the pharmaceutical market.

Fifty-five completed questionnaires were received by the end of July 2008, representing a response rate of 55.5%. However, every completed questionnaire did not include a response to every question, and percentage figures are calculated in relation to the number of responses to each question.

Results

Fifty-five countries responded to the survey questionnaires and are depicted in figure 1.

Overview of Pharmacovigilance Programmes

Seven responding countries, Bangladesh, Ecuador, Liberia, Malawi, Mauritius, Timor Leste and United Arab Emirates, indicated they have no designated pharmacovigilance system. Six percent (n = 3) of the remaining centres were established before 1990, 45% during the 1990s and 49% later. Most national centres (70%, n = 31) are affiliated with their Drug Regulatory Agency, 20% with the Ministry of Health and 10% with a university or other scientific body. In one of the responding countries the pharmacovigilance national centre was managed by an international co-operation programme of nine countries. Only 23 countries (47%) had a budget for pharmacovigilance activities and in many instances their funding was part of the general budget for drug regulatory activities, not specifically earmarked for pharmacovigilance.

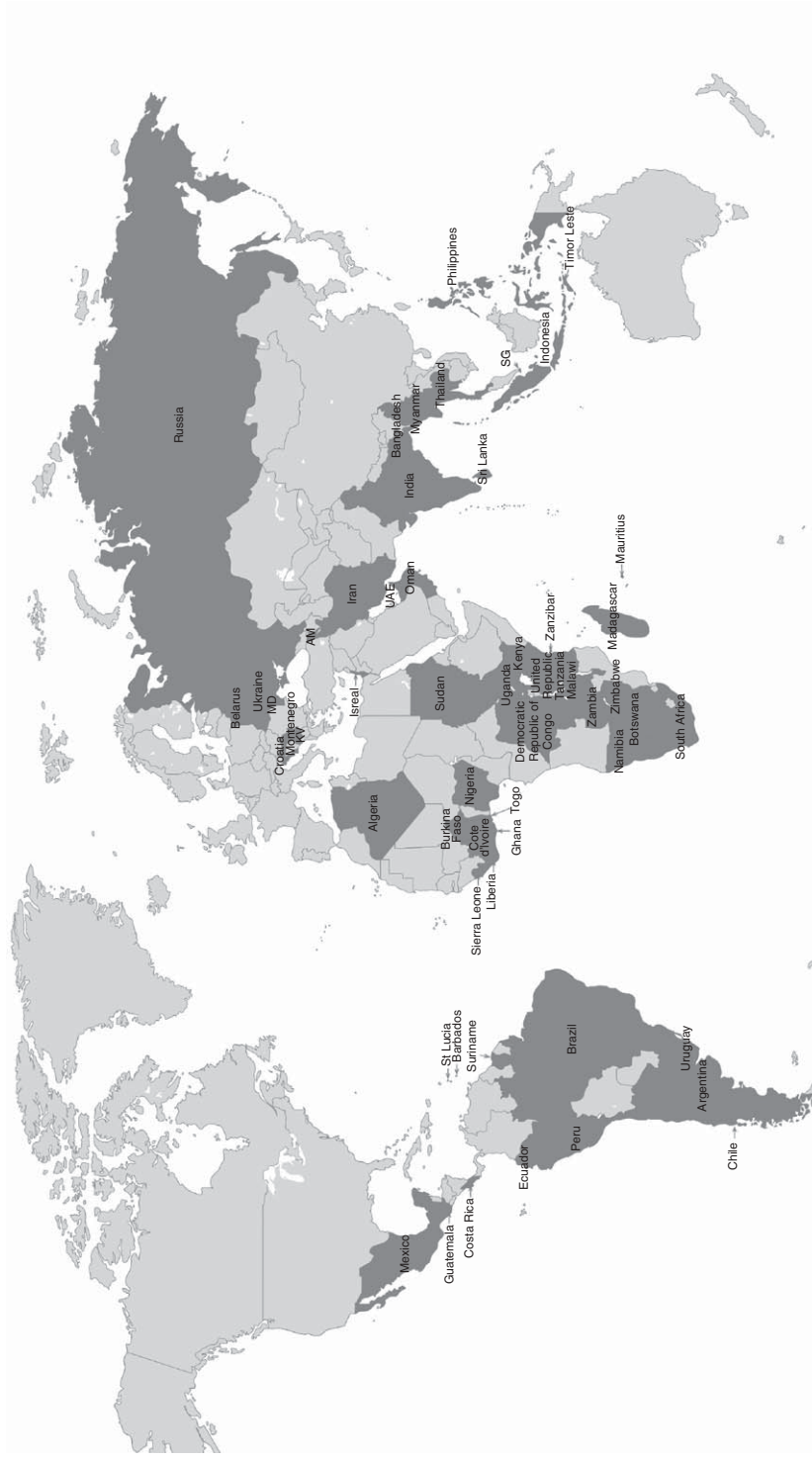

Fig. 1. Countries responding to the questionnaire (dark grey areas).

Public health programmes (44%, n = 15), the Global Fund to Fight AIDS, Tuberculosis and Malaria (36%), universities (26%), poison centres (21%), Management Sciences for Health (18%) and Rational Use of Drugs networks (15%) were cited as sponsoring some pharmacovigilance activities.

In 60% (n = 28) of responding countries there was a centralized pharmacovigilance system, while 40% had established regional centres or sentinel sites. In 80% (n = 35) of responding countries individual case safety reports (ICSRs) are submitted from the whole country, while 20% of centres cover only a limited geographical area. Most centres are inadequately staffed; six countries mentioned having only 1 staff member at the centre, 17 centres mentioned between 2 and 4 staff members per centre, 14 countries referred to having 5–9 staff members, three other countries each recorded having 10–19 staff members, 2 centres noted 20–29 staff members per centre, while another three reported having a staff size of >30.

Information Technology, Internet Support and Access to Reference Information

Although all but two centres reported having access to computer support for their activities, only eleven countries have computers specifically designated for use in pharmacovigilance. Additionally, 11 countries regarded their computer capacity as being inadequate for their needs. The great majority of centres (98%, n = 47) stated having access to telephone, 94% to e-mail, 92% to an Internet connection (several with slow connectivity) and 81% to facsimile (fax) machines. Sixty-eight percent of centres (n = 32) claimed they had adequate access to drug safety reference books either through a local library or the Internet.

Spontaneous Reporting

Types of Activities

In six countries (13%) the national centres focus their activities only on pharmacovigilance. The remaining centres are also involved in other activities such as drug information (63%), promoting patient safety (52%), rational use of drugs (46%) and poison information (15%). Some countries have a particular focus to their pharmacovigilance activities (see figure 2). In 13 countries the focused activities are integrated with the general pharmacovigilance system, to some extent in 17 and not at all in 11.

Who Reports

In 33 countries (67%) there is a legal requirement for marketing authorization holders to send ICSRs of suspected adverse drug reactions to the drug regulatory authority; in eight countries (17%) there is such a legal requirement also for healthcare professionals. In all countries that participated in the survey, physicians are encouraged to report ICSRs to the national pharmacovigilance system; and in 98% (n = 47) of the countries, pharmacists are also encouraged to report ICSRs. Other groups that are encouraged to report are nurses (90% of the responding

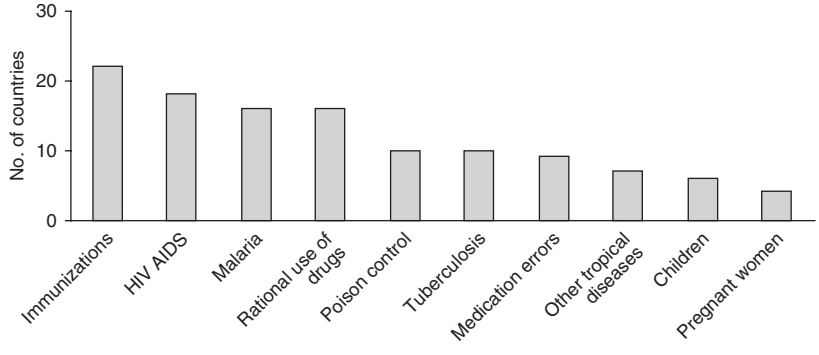

Fig. 2. Groups/areas receiving special focus.

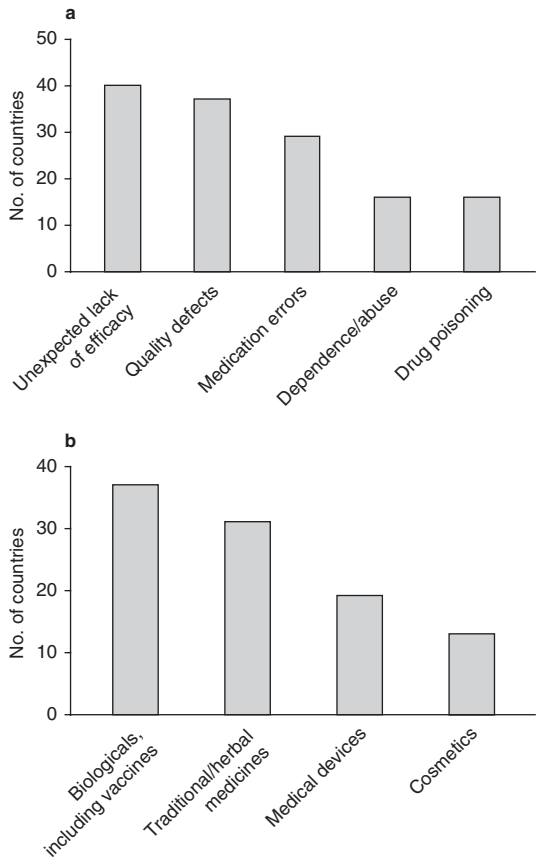

Fig. 3. (**a**) Additional problems reported through Pharmacovigilance Centres. (**b**) 'Other Products' monitored by Pharmacovigilance Centres.

countries), manufacturers (79%), patients (58%) and traditional therapists (38%).

What is Reported

In addition to reports of suspected adverse drug reactions, many pharmacovigilance systems also request case reports on other problems related to medicines (figure 3a); products other than regular pharmaceuticals are also often included in the reporting system (figure 3b). In 72% (n = 34) of countries with a reporting system a single, unique reporting form is employed, while 28% are using different forms for different kinds of problems or situations.

The number of ICSRs received by the pharmacovigilance programme for each country in 2007 varied. A majority (72%, n = 30) received <1000 reports in 2007. Mexico, Singapore and Thailand received >10 000 reports in this year (see table I). Only six countries reported a cumulative number of ≥20 000 ICSRs in their databases. For 22 countries, the cumulative number of reports in their databases was <1000.

In 25 countries (51%) there is a legal requirement for marketing authorization holders to submit periodic safety update reports.

Distributing and Returning Reporting Forms

Figures 4a and b show the most commonly used methods for distribution of ICSR reporting forms and for returning completed forms, respectively.

Data Management

Centres differ considerably regarding the available facilities for the data management of ICSRs, as indicated in figure 5. Countries with relatively few reports in a year usually do not use or require a computerized system for their data management (n = 11).

Acknowledgement, Causality Assessment, Additional Information

Only 61% (n = 28) of the national pharmacovigilance centres provide reporters with an acknowledgement of received ICSRs. Acknowledgements are provided either by telephone, letter, e-mail or cellular phone text messages (SMS). Many national pharmacovigilance centres (89%, n = 41) state that they contact reporters to acquire additional case details, usually by telephone. Sixty-two percent (n = 29) of national centres make an assessment of the likelihood of causality between the medication and the suspected adverse

Table I. Reports in 2007 and cumulative number of reports in the national database

No. of reports	No. of countries (% of respondents)	
	2007	cumulative
0–99	15 (36)	7 (20)
100–999	15 (36)	15 (43)
1000–9999	9 (21)	4 (11)
10 000–19 999	3 (7)	3 (9)
≥20 000		6 (17)

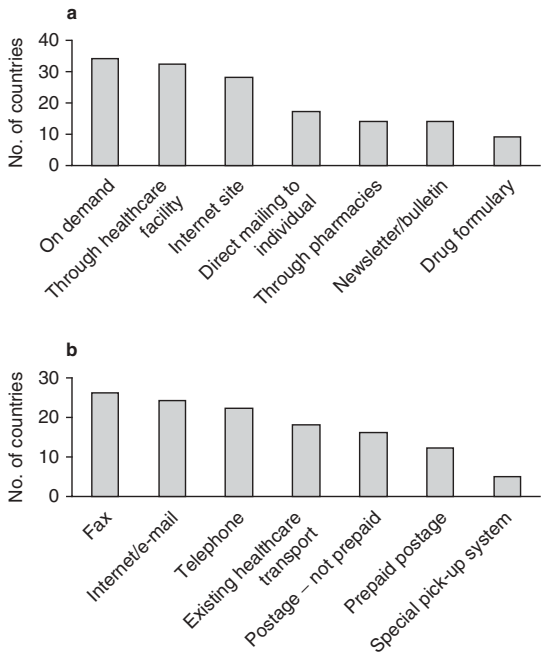

Fig. 4. (**a**) Distribution method for individual case safety report (ICSR) forms. (**b**) Return method for ICSR forms.

reaction for all ICSRs received. An additional 15% of centres carry out such causality assessments in specific situations, e.g. for serious reactions. In 54% (n = 26) of countries an Adverse Reactions Advisory Committee has been established to support the national centre staff and the drug regulatory authority.

Advocacy

Activities to advocate and promote ICSR reporting include the following: training and sensitization lectures for healthcare professionals (41 countries, 89%); articles in professional journals or newsletters (n = 25); articles or programmes in general media (n = 13); inclusion of pharmacovigilance in professional curricula (n = 19); involvement of Professional Health Organizations (n = 21); e-mail, Internet (n = 26), specific sessions at conferences (n = 30); and benefits for reporters such as continuing education points (n = 8).

Sentinel Sites and Active Surveillance

Sentinel sites[1] exist in 16 countries (34%). These sentinel sites serve to monitor HIV/AIDS patients (7 countries); children (n = 5); pregnant women (n = 3); persons with malaria (n = 3); persons with renal or hepatic failure (n = 1); persons with tuberculosis (n = 1); and insulin-dependent persons (n = 1). Specific medicines being monitored include anti-malarials (6 countries), anti-retrovirals (4 countries), anti-epileptics in pregnancy (1 country), anti-tuberculosis medicines (1 country) and vaccines (1 country).

Active surveillance[2] studies are being carried out in 18 countries (41%), with the intensive monitoring of patients admitted to a hospital being the most commonly mentioned surveillance (9 countries). A variety of specific medicines are being subjected to active surveillance studies, the most common being anti-retrovirals (9 countries), vaccines (5 countries) and anti-malarials (4 countries).

Registries for Pharmacovigilance

Pregnancy exposure registries that are designed to study the safety of medicine use during pregnancy exist in four countries (8%): Argentina (for thalidomide and isotretinoin exposures),

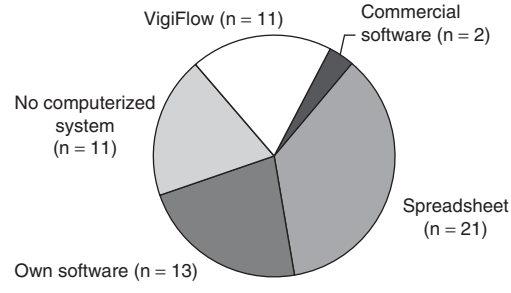

Fig. 5. Data management.

1 For the purpose of this survey, sentinel sites are defined as clinics or hospitals where a pilot programme takes place, usually to serve a particular population or to manage a particular illness/disease.

2 In this survey, active surveillance is defined as the periodic follow-up of patients undergoing drug treatment where the number of persons exposed to a medication is known and recorded.

Belarus (antiepileptic drugs), Singapore (isotretinoin) and Zambia (antimalarials). Twenty-three countries (53%) stated that they plan to set up pregnancy registries within the next 2 years. Nineteen countries (43%) responded that registries for other populations or patient groups either exist or are being planned for the purpose of studying the safety of medicines.

Drug Utilization Statistics

Twenty-three countries (51%) responded that they have some source of drug utilization statistics; others either did not have such a source or did not know if such a source existed in their country.

Use of Information from Pharmacovigilance Activities

Countries reported that information gathered through pharmacovigilance activities is used to assist regulatory functions (88%, n = 42), advise public/consumer groups (n = 20), used to develop Essential Medicines Lists (n = 19) and national drug therapeutic guidelines (n = 22) and/or shared with public health programme managers (n = 29), manufacturers (n = 26), healthcare professionals/drugs and therapeutics committees (HCPs/DTCs [n = 30]) and drugs/poisons information centres (n = 29). Table II provides information on how many labelling changes, safety warnings and market withdrawals had been made in 2007 as a result of information collected by the pharmacovigilance system in the country.

Most countries provide some form of information to the reporters, either through newsletters/information bulletins (66%, n = 29), professional journals (n = 21), at conferences (n = 28), through media (n = 17) and Internet websites (n = 22), some provide targeted messages for consumers (n = 9), and some do not share the information at all (n = 3).

Challenges and Future Activities

Respondents were asked to identify challenges in implementation, or if a programme is implemented, in the further development of pharmacovigilance. Commonly mentioned was a lack of training, poor medicine safety reporting culture and lack of funding (figure 6a). Consistent with these responses, the question on the type of assistance needed to establish an efficient and effective pharmacovigilance programme in the country identified training, technical assistance and funding as key areas requiring support in many countries (figure 6b).

Discussion

This study provides an overview of the current status of pharmacovigilance programmes in low- and middle-income countries. It demonstrates that despite its inception in the 1960s and having become firmly established in industrialized countries, pharmacovigilance is still a relatively new concept in many low- and middle-income countries. While all but seven of the responding countries indicated the presence of a designated pharmacovigilance programme, considerable variations and gaps exist in the pharmacovigilance infrastructure, resources and methodologies. Only 6% of the countries established a functional national pharmacovigilance centre from before 1990, while 50% of the countries developed their centres in this century. The number of reports in the WHO global ICSR database as well as the number of countries joining the WHO Pharmacovigilance Programme have both shown an increase only in recent years (www.who-umc.org), further illus-

Table II. 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			

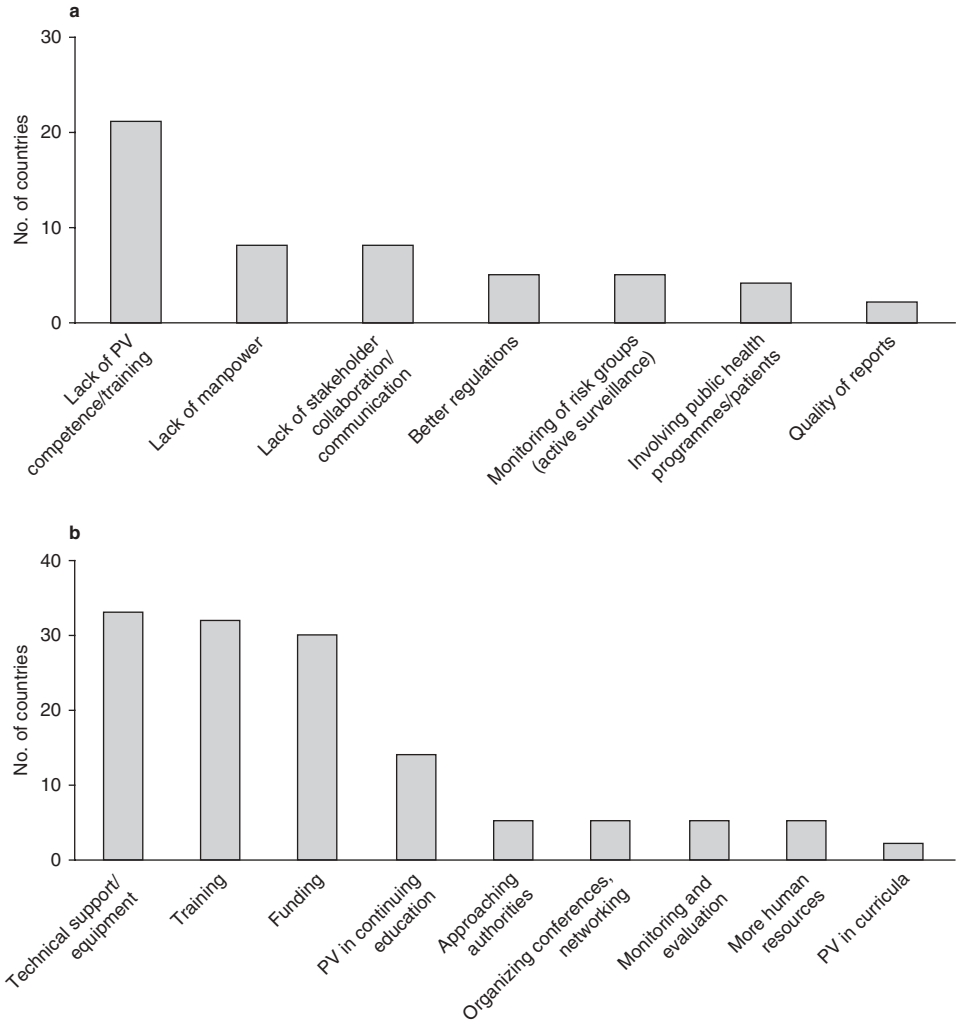

Fig. 6. (**a**) Challenges to pharmacovigilance (PV) and (**b**) type of assistance needed.

trating that pharmacovigilance has gained wide global interest only since the 1990s.

Reasons behind a Slow Growth

The successful introduction of pharmacovigilance is facilitated by a firm institutional base and solid political and financial support. Although as many as 69% of countries in this study claimed that pharmacovigilance is covered in the national legislation, we have limited information about the strength and focus of this legislation. Pharmacovigilance centres have been established within the National Drug Regulatory Agency or Ministry of Health in 49 of the countries responding to the survey. It is noteworthy that only 23 countries reported having a budget for pharmacovigilance activities, often as one of many activities to be carried out from within the budget of their regulatory authority. In over 80% of the countries assessed, the total number of health professionals engaged in pharmacovigi-

lance activities was less than ten. Support systems for staff remain weak as there are inadequate resources for data management and many countries continue to rely on relatively simple and old fashioned data systems with little or no source of funding. It would appear that pharmacovigilance activities are a low priority in most of the countries included in our survey, although an understanding of the overall infrastructure and capacity of the regulatory authority in these settings would help put the current information in better perspective.

Low Number of Reports for Signal Detection

Since ICSR reporting is based on an understanding of the significance of reporting by healthcare workers, considerable promotional efforts and time are needed to achieve high reporting rates. Our study found that 35% of countries receive less than 100 ICSRs/year. This is not a sufficient number to identify significant drug-related problems. These countries should use the WHO global database (Vigibase) frequently as a reference source for reported drug problems. However, this source might not always be relevant for the local situation. In those instances it might be useful to set up collaborative efforts across countries, where the expertise in one country could help build technical capacity in another, with the ultimate goal of consolidated reporting to the global database. It is important that data from smaller countries with similar demographics, genetic background, nutritional status and background co-morbidity all end up in one data repository, for meaningful analysis of the accumulated data for relevant solutions to priority needs of those countries.

Expanding the Scope of Pharmacovigilance

Traditionally pharmacovigilance centres have focused on capturing the adverse events related to the intrinsic nature of the medicine. However, in following the WHO definition of pharmacovigilance,[3] the centres invariably capture all kinds of drug-related problems, including unexpected lack of efficacy, quality defects, drug abuse, medication errors and poisonings that are not necessarily related solely to the nature of the medicines. The study shows 40 countries capturing events related to unexpected lack of efficacy, events that could be due to quality defects, counterfeiting, antibiotic resistance, irrational drug use and/or inadequate quality of patient care. This points to a need for strengthening in-country expertise in evaluating these reports through training programmes and other capacity-building activities.

Barriers to Reporting

Spontaneous reporting is based, in large part, on an understanding of the significance of reporting, therefore considerable promotional efforts and time are needed to educate the health professionals on its importance. According to this assessment, 19 countries have introduced pharmacovigilance as part of medical education. This is very encouraging, particularly when considering that pharmacovigilance in curricula is still rather uncommon in many industrialized countries.[6] Relatively few low- and middle-income countries have instituted legislations for mandatory reporting by health professionals; a measure that is relatively common elsewhere, e.g. in Europe; but the effectiveness of the regulatory intervention in improving reporting rates appears rather weak.[1] Thirty-three countries in the survey have implemented mandatory reporting by industry. However, this measure may not have had an impact on overall reporting practices, particularly since most countries have very few ICSRs in their national databases.

Frequently, physical barriers impede reporting rates. At the very least, reporting forms have to be easily available and accessible at all reporting centres. Reporting forms are often distributed through healthcare facilities and pharmacies rather than by post. The most commonly used method according to this survey is distribution on demand but this is not optimal. Forms should actively be disseminated to all facilities where

3 Pharmacovigilance – the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[5]

potential reporters are practicing to reduce barriers for reporting. Telephone/fax and Internet/e-mail constitute important reporting back routes for many pharmacovigilance systems.

Other return mechanisms use existing transport systems that are also used for other healthcare services, e.g. medicine distribution. In five countries, pharmacovigilance centres have access to vehicles and organize special report form pick-up rounds. Relatively few countries in this study have been able to organize (postage prepaid) mail return of reporting forms. The lack of prepaid postage affixed stamps to reporting forms could be an important deterrent contributing to low reporting rates. It is of some concern that only about 60% of pharmacovigilance centres provide reporters with an individual acknowledgement that a report has been received. Experience shows that such acknowledgement is vital; health professionals are not likely to maintain their reporting if they do not get confirmation that their effort is welcome and appreciated.[7,8] On the other hand, almost 90% of the centres are prepared to contact the reporter for additional details about a reported case, if needed. This 'active approach' to seek additional information can serve as a form of acknowledgement and can also lead to educational discussions about patient management and about reporting.

Incentives, Professional Benefits, Expert Advice

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations. Eight countries use continuing medical education (CME) credits for medical professionals.[9] Training, expert assistance and access to telecommunication tools and aids can not only help improve reporting rates but may also enhance the quality of reports.[10] The WHO Pharmacovigilance Programme uses a data management tool, VigiFlow, for receiving and storing adverse drug reaction reports. VigiFlow is easy to use and error checking ensures accuracy when entering reports and is currently being used by 30 countries (11 in this study). A search and statistics module is built into the system and can be used to make sophisticated comparisons and summary tabulations for periodic safety update reports. This tool has dramatically improved the ease of reporting, from regional centres to the national pharmacovigilance centre and then on to the WHO global database. WHO is also considering ways of enhancing the tool with some information on reported products, as a source of reference information for reporters.

Pharmacovigilance centres with a low rate of reporting carry out a formal causality assessment on all reports received and a further 15% apply it in special situations. These are educational functions for pharmacovigilance staff and may improve the centre's ability to counsel reporters and to focus on the most important problems. In countries with high reporting rates, causality assessments are often reserved for situations where aggregates of similar reports have been received.

Just over half of the pharmacovigilance systems (54%) have established a drug safety advisory committee to support the national pharmacovigilance centre and to give advice to the regulatory authority. Experience from industrialized countries has shown that such a committee may be very powerful in supporting and promoting patient safety activities and in providing solid scientific and clinical input to the drug regulatory process.

Traditional Practitioners and Consumers

All pharmacovigilance centres encourage health professionals to report suspected drug-related problems. However, only 38% of the countries in this study mention traditional therapists in this category. Worldwide, the use of traditional medicines has grown.[11] The safety, efficacy and quality of traditional, complementary and alternative medicines are important concerns, both for health authorities and the public.[12] Excluding the practitioners of these forms of medicines from a reporting programme leaves a gap in pharmacovigilance information.

It is encouraging to note that almost 60% of all centres in this survey encourage patient reporting. In countries where a significant part of drug distribution takes place over the counter or through unlicensed vendors it is important to bring in all stakeholders, beyond and in addition

to healthcare professionals, into the pharmacovigilance network. The public at large must be involved in the collection of information of problems related to self-medication since healthcare professionals are not likely to learn about them. It has been demonstrated in some industrialized countries – Australia, Canada, Denmark, the Netherlands, the Philippines, Sweden, the UK and the US – that including consumer organizations in the national pharmacovigilance network brings new dimensions to drug-related problems identified and described by patients themselves.[13,14] Contrary to earlier concerns, the quality of patient reports is good.[15]

Pharmacovigilance in Public Health Programmes

A positive observation in this assessment is that public health programmes (see figure 2) and donor organizations have now also become engaged in supporting pharmacovigilance in these programmes. This is a mutually beneficial development in that there is now a very welcome addition to the resources for pharmacovigilance, which in turn can strengthen dedicated national programmes (such as those for the control and treatment of tuberculosis, malaria and HIV/AIDS) with safety data from large treatment cohorts to support clinical decision making.[16] However, better integration is needed between patient safety activities carried out by public health and immunization programmes and those carried out by pharmacovigilance centres.

Organization and Infrastructure

Twenty percent of countries in this survey collect safety information from only a region or area of their country. Many countries, although still a minority, have set up regional pharmacovigilance centres or sentinel sites. This arrangement brings the pharmacovigilance centres closer to the professionals in practice, making it easier for them to report and exchange information.[17] Such a model in general is likely to promote reporting from various regions and help collect pharmacovigilance data that are more representative of the entire country; however, there are organizational and other features of the infrastructure (e.g. Internet connections, bandwidth) that may limit 'reporting reach' of professionals in remote parts of the country.

Sentinel Sites and Active Surveillance

Only a limited number of countries indicated their use of sentinel sites or active surveillance for pharmacovigilance, presumably because such studies require special funding, organized record keeping and methodological expertise. Vulnerable populations, such as children and women of childbearing age, excluded from clinical trials or being treated with medicines known to be associated with particular risks are included in such special studies. Ideally the introduction of new medicines in public health programmes in new populations should always be associated with sentinel site monitoring or active surveillance such as cohort event monitoring.[18]

There is a greater need to monitor and promote the safety of medicines that are subject to scale-up programmes. In addition to cohort event monitoring, the use of registries is advocated as a means of conducting targeted post-approval drug surveillance. Four countries referred to the use of pregnancy registries and several countries mention plans to set up pregnancy registries within the next 2 years.

Using Pharmacovigilance Information

Information collected in pharmacovigilance systems are most commonly used for drug regulatory activities. Virtually all countries for which such use is not mentioned have very young reporting systems. Presumably the information received is considered inadequate to trigger or support regulatory decisions. A majority of countries share pharmacovigilance information with public health programmes, drug information centres and health professionals and Drugs and Therapeutics Committees. Pharmacovigilance information is reportedly less commonly used as a background when elaborating Essential Medicines Lists, therapeutic guidelines or in providing information to the public. As mentioned above, 42 countries stated using pharmacovigilance information to support drug regulatory activities. A follow-up question

in our survey concerned the character and frequency of such activities in 2007 supported by domestic pharmacovigilance information. Answers demonstrated a very wide range of such activities, some countries took no action in 2007, while others report more than three market withdrawals in the year (see table II). No judgement can be made whether pharmacovigilance data have been under or over utilized in countries for regulatory decision making since there are vast variations in the pharmaceutical market situation and legal systems between countries. No qualitative information is available for assessing the scientific justification for the various measures taken.

Relationship with Media

Information is most commonly disseminated through printed messages in newsletters and journals for professionals, but information sharing through conferences and the Internet is also very common. Fewer countries mention using mass media (39%). Effective media relations are an essential aspect of the communications activities in pharmacovigilance. Open lines of communication with the media are likely to facilitate the creation of policies and legislation on pharmacovigilance, which will enjoy widespread public support and confidence and limit unfounded rumours and misplaced concerns about the safety of potentially valuable medicines.[19] The 1998 Erice Declaration has called for a united effort by all stakeholders for the communication of drug safety information in a transparent, equitable a credible fashion.[20] Authorities need to have a defined schedule of media relations activities, including personal contact, briefings and visits, news conferences, information packs and briefings.[21] Many regulatory authorities have now extended their communication activities, developed websites and newsletters, and have actively engaged with the media to provide the public with updated safety information (www.nafdacnigeria.org).

Pharmacovigilance Development and Implementation Challenges

Challenges to pharmacovigilance programmes and their implementation appear fairly consistent across countries. The lack of staff trained in pharmacovigilance seems to be the most serious limiting factor for the development of pharmacovigilance in low- and middle-income countries. Competencies in cross-cutting scientific areas are normally required in carrying out pharmacovigilance functions. Very few academic institutions offer any formal education in pharmacovigilance. Since pharmacovigilance has not been part of the basic training of the practicing health workers, considerable efforts are needed to promote the importance of pharmacovigilance and to instil a 'reporting culture' in these individuals. There are expectations on WHO to organize training courses and to provide technical support. WHO and UMC are already active, e.g. organizing conferences, creating international networks and approaching authorities. Additional in-country technical support for pharmacovigilance is offered by other groups, such as Management Sciences for Health through their Strengthening Pharmaceutical Systems (www.msh.org/projects/sps) initiative. Further resources are needed in these sectors to meet the requirements of countries. Several international agencies are also stepping in with various programmes and activities to support pharmacovigilance in countries. While this is a welcome development, these efforts need to be harmonized to ensure global standards and best practices in pharmacovigilance.

Lack of sufficient funding is another constraint and in turn might imply a lack of political commitment to patient safety activities in a country. Funding is particularly scarce in countries with young pharmacovigilance systems. Other areas requiring help include infrastructure, networking and communication between stakeholders. Building pharmacovigilance systems is a complex operation requiring diplomatic and persuasive skills and patience. To be successful, both a supportive regulatory system and appropriate funding are required, success factors that seem often to be missing in countries. Under these circumstances, novel models of funding need to be explored. As noted by Pirmohamed et al.,[22] building on existing structures, pooling data for broader learning, promoting public-private partnerships for pharmacovigilance of new medicines, and exchange visits to developed

countries are some ways to seed and support pharmacovigilance in developing countries.

Limitations of the Survey

The current study is limited in assuming that the respondents had full access to all relevant and current information. The authors did not verify or validate the information. For countries participating in the WHO Pharmacovigilance Programme, the authors contacted the designated pharmacovigilance representatives. For those seven countries with no pharmacovigilance centres, the authors requested information from collaborators engaged in related work within the countries. Because they had no pharmacovigilance centres, these seven countries had no information to provide except on questions related to challenges and future plans for pharmacovigilance. The questionnaire was directed at national pharmacovigilance centres, and did not target specific public health programmes. In that sense, the data collected may not reflect the true status of pharmacovigilance within the public health programmes in countries. A response rate of 55% might seem low. The authors did not investigate why some countries did not respond. However, the current return rate is consistent with results from similar exercises in the last 30 years of the WHO Pharmacovigilance Programme (unpublished data). It is possible that the characteristics (national income, healthcare expenditure, age of the pharmacovigilance system etc.) of those countries that responded differ from those that did not. However, such a differential analysis has not been carried out in this investigation. Therefore, the current conclusions on pharmacovigilance status may not apply to countries that did not participate in the survey.

Conclusions

This assessment has helped define the pharmacovigilance status in 55 low- and middle-income countries across the world. Some of the special challenges and barriers to promoting pharmacovigilance in these settings have been identified and will form the bedrock of a pharmacovigilance strategy for these countries. 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.

Acknowledgements

The authors are indebted to all the National Pharmacovigilance Centre representatives who participated in this survey. The departments of Epidemiology and Global Health at the School of Public Health, University of Washington, Seattle, WA, USA, where Andy Stergachis is affiliated, were supported in part by the Bill and Melinda Gates Foundation via the University of Washington. Andy Stergachis' departments have received a grant via Managements Sciences for Health-United States Agency for International Development (MSH-USAID) for Strengthening Pharmaceutical Systems. No other sources of funding were used to assist in the preparation of this study. None of the other authors have any conflicts of interest that are directly relevant to the content of this study.

References

1. Olsson S, editor. National pharmacovigilance systems. 2nd ed. Uppsala: The Uppsala Monitoring Centre, 1999
2. Ratanawijitrasin S, Wondemagegnehu E. Effective drug regulation: a multi-country study. Geneva: WHO, 2002
3. Hughes ML, Whittlesea CMC, Luscombe DK. Review of national spontaneous reporting schemes: strengths and weaknesses. Adv Drug React Toxicol Rev 2002; 21: 231-41

4. Sachdev Y. Status of adverse drug reaction monitoring and pharmacovigilance in selected countries. Indian J Pharmacol 2008; 40 Suppl. 1: S4-9
5. World Health Organization. The importance of pharmacovigilance. Geneva: WHO, 2002: 42
6. Lo Re 3rd VL, Strom BL. The role of academia and the research community in assisting the food and drug administration to ensure US drug safety. Pharmacoepidemiol Drug Saf 2007 Jul; 16 (7): 818-25
7. Biriell C, Edwards IR. Reasons for reporting adverse drug reactions: some thoughts based on an international review. Pharmacoepidemiol Drug Saf 1997; 6: 21-6
8. Bukirwa H, Nayiga S, Lubanga R, et al. Pharmacovigilance of antimalarial treatment in Uganda: community perceptions and suggestions for reporting adverse events. Trop Med Int Health 2008; 13 (9): 1143-52
9. Encheva D. Spontaneous reporting and continuing medical education. Uppsala Rep 2004 Apr; 25: 10-1
10. Sevene E, Mariano A, Mehta U, et al. Spontaneous adverse drug reaction reporting in rural districts of Mozambique. Drug Saf 2008; 31 (10): 867-76
11. World Health Organization. National policy on traditional medicine and regulation of herbal medicines: report of a WHO global survey. Geneva: WHO, 2005
12. World Health Organization. WHO traditional medicine strategy: 2002-2005. Geneva: WHO, 2002
13. Medawar C, Herxheimer A. A comparison of adverse drug reaction reports from professionals and users relating to risk of dependence and suicidal behaviour with paroxetine. Int J Risk Saf Med 2004; 16 (1): 5-19
14. Australian Council for Safety and Quality in Health Care. Partnerships for health in action: promoting consumer and community involvement in healthcare improvement. Canberra (ACT): Australian Council for Safety and Quality in Health Care, 2005
15. van Grootheest K, Graaf L, Lolkje TW, et al. Consumer adverse drug reaction reporting: a new step in pharmacovigilance. Drug Saf 2003; 26 (4): 211-7
16. World Health Organization. The safety of medicines in public health programmes: pharmacovigilance an essential tool. Geneva: WHO, 2006
17. Shin YS, Lee YW, Choi YH, et al. Spontaneous reporting of adverse drug events by Korean regional pharmacovigilance centers. Pharmacoepidemiol Drug Saf 2009 Oct; 18 (10): 910-5
18. World Health Organization. A practical handbook on the pharmacovigilance of antimalarial medicines. Geneva: WHO, 2007
19. Dodoo A, Adjei S, Couper M, et al. When rumours derail a mass deworming exercise. Lancet 2007; 370: 465-6
20. The Uppsala Monitoring Centre. Dialogue in pharmacovigilance: more effective communication. Uppsala: Uppsala Monitoring Centre, 2002
21. The Uppsala Monitoring Centre. Expecting the worst: anticipating, preventing and managing medicinal product crises. Uppsala: Uppsala Monitoring Centre, 2003
22. Pirmohamed M, Atuah KN, Dodoo A, et al. Pharmacovigilance in developing countries. BMJ 2007; 335: 462

Correspondence: Mr *Sten Olsson*, WHO Collaborating Centre for International Drug Monitoring, Box 1051, S-751 40 Uppsala, Sweden.
E-mail: sten.olsson@who-umc.org