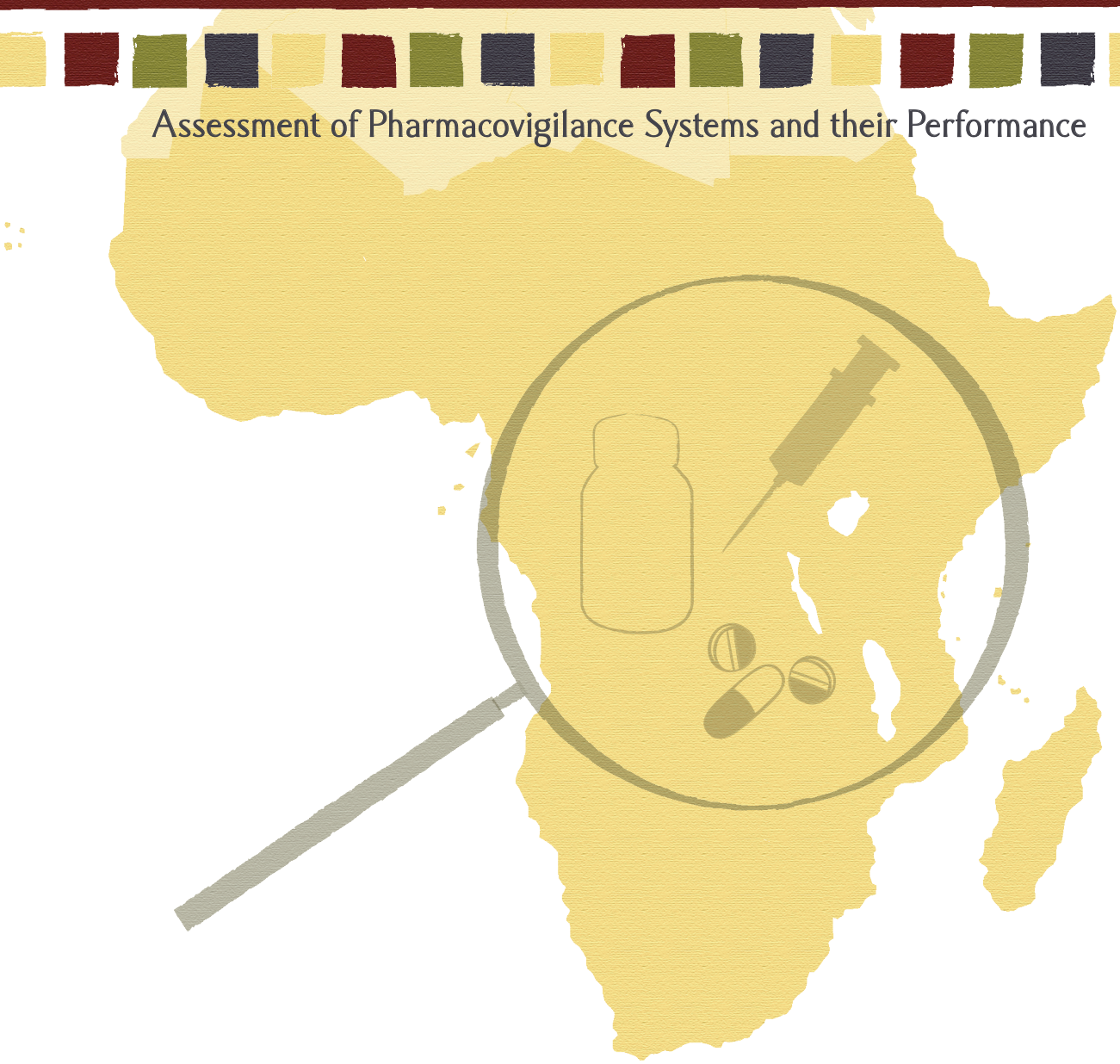
Safety of Medicines in Sub-Saharan Africa

Assessment of Pharmacovigilance Systems and their Performance



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The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

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Strengthening Pharmaceutical Systems
Center for Pharmaceutical Management
Management Sciences for Health
4301 North Fairfax Drive, Suite 400
Arlington, VA 22203 USA
Telephone: 703.524.6575
Fax: 703.524.7898
E-mail: sps@msh.org
Web: www.msh.org/sps

Foreword

Access with Pharmacovigilance—Ensuring that Patient Safety is Not Subordinate to Access

> ...the Panel sees a need for the organization to require PRs (Principal Recipients) to invest more of grant budgets, systematically, in pharmacovigilance programs that monitor the quality, usage and efficacy of the drugs it buys, and that can track adverse events among patients and other post-marketing product defects.
>
> — The Final Report of the High-Level Independent Review Panel on Fiduciary Controls and Oversight Mechanisms of the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Adverse drug events (ADEs) from poor product quality, adverse drug reactions (ADRs), and medication errors contribute significantly to morbidity and mortality. Though most cases go undetected particularly in developing countries, data from the US estimates that ADEs are the fourth to sixth leading cause of death. The well-known cases of product quality associated with diethylene glycol led to more than 700 reported deaths in nine countries including two occurrences in Nigeria and a 1987 case in South Africa. ADEs constitute a huge cost to the health system, estimated in the US at $177.4 billion in 2000. Economic consequences of adverse events that are not frequently reported include the impact of adverse events on patient adherence to treatment, drug resistance, and treatment outcomes. Besides the economic consequences, cases of adverse events affect the credibility of the health system leading to loss of confidence.

The time to confront the epidemic of harm from medicine use is now. Access to medicine is improving globally. New medicines are being introduced, and more people are being exposed to those new medicines and vaccines. A key responsibility of national regulatory authorities is to safeguard the public health of the citizens. To do this, the regulatory authorities need to work closely with all stakeholders and more so with global health initiatives contributing to improving access. Pharmacovigilance is not a luxury for Africa, it is not to be thought of as a distraction, and it is not to be subordinate to access. There could not be a better time for this assessment on the drug safety systems and their performances in sub-Saharan Africa.

The 2007 World Health Assembly resolution on rational use of medicines states that irrational use continues to be an urgent and widespread problem in the public and private health sectors in developed and developing countries resulting in serious consequences in terms of poor patient outcome, ADRs, increasing antimicrobial

resistance, and wasted resources. This study exposes how countries are struggling in addressing ADRs at health facilities. Recommendation #6, "Get Serious About Results", from the panel report quoted above recommends that the Global Fund implement more-rigorous pharmacovigilance of drugs purchased with Global Fund resources, both at national and international levels, to ensure compliance with the organization's Quality Assurance policy and track side-effects. The same message should go not only to the Global Fund but to all donors. To the African regulatory authorities, the message is also the same; it is time to get serious about their mandate to protect the public health of their citizens.

Margareth Ndomondo-Sigonda
African Medicines Regulator

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Acronyms and Abbreviations

ACT	artemisinin-based combination therapy
ADE	adverse drug event
ADR	adverse drug reaction
AEFI	adverse events following immunization
AERS	Adverse Event Reporting System
AFSSAPS	L'agence Francaise de Securite Sanitaire des Produits de Sante (French Health Products Safety Agency)
AMFm	Affordable Medicines Facility-malaria
AMRH	African Medicines Registration Harmonisation
ART	antiretroviral therapy
ARV	antiretroviral
BCPNN	The Bayesian Confidence Propagation Neural Network
BMGF	Bill & Melinda Gates Foundation
CEDIM	Centre de Documentation et d'Information sur le Médicament, Burkina Faso
CEM	cohort event monitoring
CHMP	Committee for Medicinal Products for Human Use
CNPV	National Centre for Pharmacovigilance, DRC
CRO	clinical research organization
DEG	diethylene glycol
DGPML	Direction Générale de la Pharmacie, du Médicament et des Laboratoires, Burkina Faso
DPL	Direction de la Pharmacie et des Laboratoires, Senegal
DPM	Direction de la Pharmacie, Médicaments et Plantes médicinales, DRC
DRC	Democratic Republic of the Congo
DTC	Drug and Therapeutics Committee

EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GAVI	Global Alliance for Vaccines and Immunization
GDP	gross domestic product
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INESS	INDEPTH Effectiveness and Safety Studies of Antimalarials in Africa
IPAT	indicator-based pharmacovigilance assessment tool
LOC	locally owned companies
MAH	marketing authorization holder
MCC	Medicines Control Council, South Africa
MedDRA	Medical Dictionary for Regulatory Activities
MGC	multinational generics companies
MIC	multinational innovators companies
MSH	Management Sciences for Health
NAFDAC	National Agency for Food and Drug Administration and Control [Nigeria]
NDA	National Drug Authority [Uganda]
NMCP	National Malaria Control Program
NMP	national medicines policy
NMRA	national medicines regulatory authority
NPC	National Pharmacovigilance Center
NTD	neglected tropical disease
OECD	Organisation for Economic Co-operation and Development
PEPFAR	President's Emergency Plan for AIDS Relief
PHP	public health program
PMI	President's Malaria Initiative
PPB	Pharmacy and Poisons Board, Kenya
PQM	Promoting the Quality of Medicines [USAID]
PRs	principle recipients
PSUR	periodic safety update report
PV	pharmacovigilance
RBM	Roll Back Malaria
RMP	risk management plan

SAE	serious adverse event
SOP	standard operating procedure
SPS	Strengthening Pharmaceutical System
SRA	stringent regulatory authority
SSA	sub-Saharan Africa
TB	tuberculosis
TFDA	Tanzania Food and Drugs Authority
TPE	total pharmaceutical expenditure
UMC	Uppsala Monitoring Centre [WHO]
UMC-Africa	WHO Collaborating Center for Advocacy and Training in Africa
USAID	US Agency for International Development
USD	US dollars
USP	United States Pharmacopeia
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

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Authors

Hye Lynn Choi, Program Associate, SPS Program, MSH

David Lee, Director Technical Strategy and Quality, Center for Pharmaceutical Management, MSH

Jude Nwokike, Principal Technical Advisor/Regulatory Affairs, SPS Program, MSH

Contributors

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Angola
Raquel Barrientos

Benin
Benoit Hounkpevi, Delphin Degla

Botswana
Pauline M. Tsiu, Lebogang Koitsiwe

Burkina Faso
Jean-Baptiste Nikiema, Arsène Ouedraogo, Claude Roger Ouandaogo (Direction Générale de la Pharmacie, du Médicament et des Laboratoires); Lassané Kaboré (data collector)

Burundi
Deo Niyonzima, Emmanuel Maregeya, Diane Ndayiragije

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Yayo S. P. Olivier

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Kipkerich Chumo Koskei (Ministry of Medical Services); Fred Siyoi, Jayesh Pandit, Dominic Kariuki, Edward Abwao, Stephen Kimatu (Pharmacy and Poisons Board); Mary Wangai, Ndinda Kusu, Patrick Boruett, and Lillian Gitau (SPS)

Madagascar
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Rwanda
Gege Buki, Anicet Nyawakira

Senegal
Papa Amadou Diop, Birame Dramé (Directeur de la Pharmacie et des Laboratoires); Mamadou Cisse (consultant); Serigne Diagne, Suzanne Diarra (SPS)

South Africa
Caroline Adam (consultant to SPS for pharmacovigilance); Jean-Pierre Sallet, Fathima Fyzoo, Gavin Steel, and Tiwonge Mkandawire (SPS)

Sudan
Tesfaye Godana Amare

Tanzania
Mitangu A. Fimbo, Henry Irunde, Alambo Msusa, Grace Mngo'ng'o Shimwela, Sunday Kisoma, Yonah Hebron, James Ndege (Tanzania Food & Drugs Authority); Michael Gabra, Salama Mwakisu, Vincent Manyilizu (SPS)

Togo
Amavi Edinam Agbenu

Uganda
Martin Olowo Oteba, Thomas Obua (Pharmacy Division, Ministry of Health); Gordon Sematiko Katende, Gabriel Kaddu, Helen Byomire Ndagije, Moses Ogaa, David Nahamya, Wilberforce Kwiringira, Huldah Nassali, Victoria Nambasa Bukenya (National Drug Authority); Birna Trap, Saul Kidde, Loi Gwoyita (MSH/Securing Ugandans' Right to Essential Medicines Program)

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University of Washington, Seattle, WA
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Executive Summary

With increased access to new essential medicines, such as artemisinin-based combination therapy (ACT) and antiretroviral (ARV) therapy in Africa, there is a greater need to monitor and promote safety and effectiveness of medicines. The burden of adverse events from poor product quality, adverse drug reactions (ADRs), and medication errors may affect achieving the full benefits of these new medicines and pose great challenges to health care systems in Africa. Besides the impact of adverse drug events (ADEs) on morbidity and mortality and the direct cost of managing the events, ADEs also have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance. Although it is challenging to measure these costs, it is apparent that they may constitute a profound impact on the resources of the health system.

The pharmacovigilance (PV) system safeguards the public through efficient and timely identification, collection, assessment, and communication of medicine-related adverse events. A comprehensive PV system includes both active and passive surveillance methods, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of PV activities into the various levels of the health system, from the facility to the national levels.

The objectives of this study were to—

- Provide a comprehensive description and analysis of national PV systems in sub-Saharan African (SSA) countries
- Identify replicable and successful experiences and classifying countries based on performance
- Map out how donor agencies and global health efforts are contributing to PV in SSA countries
- Recommend options for enhancing PV systems

The study used 3 methods to assess PV systems and their performance in 46 SSA countries: literature review, mailed survey, and in-depth assessment that was administered by consultants who visited 9 priority countries—Burkina Faso, Democratic Republic of Congo, Ghana, Kenya, Nigeria, Senegal, South Africa, Tanzania, and Uganda. The Indicator-based Pharmacovigilance Assessment Tool (IPAT) was adapted and used for data collection.

Below are the highlights of findings on the current state of PV systems and performance in 46 SSA countries and recommendations for strengthening their regulatory capacity for monitoring safety and quality of medicines in the supply chain.

Current State of PV Systems in Sub-Saharan Africa

With an estimated pharmaceutical market size of 3.8 billion to 4.7 billion US dollars (USD) and local manufacturing capacity in 80 percent of countries, capacity for regulating health products in SSA is inadequate. Currently, 74 percent of these 46 countries have a national medicines regulatory authority (NMRA), 78 percent have a national medicine policy (NMP), 5 World Health Organization (WHO) prequalified quality control laboratories exist in the region, and 33 SSA countries are an official or associate member of the WHO Programme for International Drug Monitoring.

Components of PV

Policy, Law, and Regulation

Of the 46 SSA countries, 41 percent have a national policy related to PV and medicine safety; 30 percent provide a legal mandate to monitor medicine-related adverse events. Only 28 percent of countries have legal provisions that require marketing authorization holders (MAHs) to report all serious ADRs to the NMRA and 17 percent require MAHs to conduct post-marketing surveillance activities. The lack of relevant policy and regulations in SSA reflects fundamental limitations for enforcing medicine safety monitoring.

System, Structure, and Stakeholder Coordination

Of the SSA countries, 74 percent have a PV center or unit with a clear mandate and formal organizational structure, 39 percent have national PV guidelines, 39 percent have a safety advisory committee, and 45 percent have a drug information service. However, country coordination of all stakeholders is minimal—only 28 percent have a platform or strategy to coordinate PV activities at the national level.

Signal Generation and Data Management

The scope of PV is limited in most of the SSA countries. Although 74 percent have spontaneous reporting systems, less than 50 percent monitor product quality, medication errors, and treatment failures through existing systems. A PV database exists in 50 percent of the countries, but coordination and collation of PV data from all sources was inadequate.

Risk Assessment and Evaluation

The reporting rate is minimal in most SSA countries; only 2 of the countries surveyed collected more than 100 reports per million population in 2010, and most countries generated less than 20 reports per million population per year. The capacity to conduct medicine safety research exists in Africa, yet active approaches to identify and evaluate medicine-related risks are limited. In the last 5 years, only 48 percent of countries conducted active surveillance activities, 28 percent carried out drug use studies, and only 37 percent conducted product quality surveys.

Risk Management and Communication

Of 46 SSA countries, 20 percent published medicine safety newsletters, 33 percent distributed safety alerts, and 37 percent took at least one form of regulatory action as a result of PV activities in 2010. Of the regulatory actions taken, 68 percent were concerned with safety, 29 percent with product quality, and 3 percent with rational use issues. Some countries have used the safety information from external sources to enact regulatory measures but sporadically. Less than 20 percent of product safety issues identified by stringent regulatory authorities that are relevant in the local context—products are registered and in use in their own country and have important public health implications—were reviewed and acted on in most countries. Most of the countries did not have procedures for managing or minimizing important known harmful effects of high-risk medicines. There was no formal risk management activity designed to prevent or minimize problems related to the medicine. The study found risk management and communication as the PV component with the weakest system and performance.

PV in Public Health Programs

We studied 32 public health programs (PHPs) including HIV/AIDS, malaria, tuberculosis (TB), and immunization programs in the selected countries. Among 32 PHPs, 12 programs have policy statements on PV and15 programs have a unit or focal person for PV. The policy framework and basic structures were more likely to be found in malaria and immunization programs than in HIV/AIDS and TB programs. There was little effort to routinely collate and aggregate adverse events and treatment modification data in PHPs and to share the information with national PV centers; only 10 programs routinely collect data on adverse events. More programs for malaria and immunization in particular are now implementing active surveillance with financial and technical support from global health initiatives. Risk management activities were lacking across all PHPs.

Patient Safety and PV

A total of 54 Drug and Therapeutics Committees (DTCs) in the selected countries were visited for this study. Most DTCs have not implemented interventions to improve patient safety although they are mandated to do so. On average, less than 40 percent of DTCs have implemented active approaches to monitor and investigate adverse events in the last 5 years, 47 percent reviewed ADR reports and addressed medicine safety issues, and 23 percent took any action related to medicine safety in 2010.

PV in Pharmaceutical Industry

Regulations to enforce the responsibilities of pharmaceutical industry with regards to safety reporting are lacking in most countries. Consequently, pharmaceutical industry involvement in PV was minimal. Of 21 pharmaceutical companies including multinational and locally owned companies studied in the selected countries, only 8 have a unit or staff responsible for PV activities, 5 have a standard operating procedure (SOP) or reporting form for PV, and 3 conduct post-marketing surveillance activities. Pharmaceutical companies in South Africa show some encouraging trends in PV development in terms of structure, designated staff, and SOPs, although the functions were often limited to collecting and reporting the adverse events and not expanded to risk evaluation and decision making. In general, awareness on national PV systems, guidelines, regulations, or ADR forms was low.

Capacity of PV Systems in SSA

WHO defines the minimum requirements for a functional national PV system as having a national PV center, a spontaneous reporting system, a national database, a national PV advisory committee, and a communications strategy. To build on these minimum requirements and highlight the need for providing further details and indicators for monitoring all aspects of comprehensive PV systems and benchmarking these systems' performance, we developed the systems classification. This classification represents the level of systems' capacity and performance for meeting relevant indicators in five components: (1) policy, law, and regulation; (2) system, structure, and stakeholder coordination; (3) signal generation and data management; (4) risk assessment and evaluation; and (5) risk management and communication. Countries are classified into four groups based on the findings related to the capacity and performance of their PV systems—

- **Group 1—Countries have no capacity or only minimal capacity for PV.** There are no legal or structural frameworks for PV systems and no coordinated passive or active surveillance in these countries. Any ongoing PV activities take place without national coordination. Twenty-four SSA countries are in group 1. All countries that have not joined the WHO program, except for Malawi, fall under this group.
- **Group 2—Countries have basic structure in place.** The countries have policy and legal frameworks for PV. Most basic organizational structures, such as an institution with a clear mandate for PV, guidelines and SOPs, a reporting form, and a safety advisory committee, are in place. Roles and responsibilities of stakeholders are recognized, but not fully coordinated. The capacity to generate signals and evaluate the risks is limited in these countries. The spontaneous reporting system does not cover all sources of medicines-related problems. The PV system lacks active approaches to evaluate signals and implement effective risk management practices. Sixteen SSA countries are in group 2.
- **Group 3—Countries have the capacity to collect and evaluate safety data on the basis of legal and organizational structure.** The countries have organizational structure and policy framework to collect and collate safety data in a national database and evaluate the risks and benefits by both passive and active approaches. However, the capacity to manage the risks by taking appropriate preventative actions, develop a plan to actively monitor the risks, and communicate with stakeholders is lacking. Two SSA countries are in group 3.

- **Group 4—Countries have performing PV systems to detect, evaluate, and prevent medicine safety issues.** The countries have the basic structures, both passive and active surveillance activities, and the capacity to evaluate the risks. Based on these, outcomes of PV activities inform regulatory actions and are communicated to stakeholders. Countries in this group do not necessarily reflect a perfect or ideal PV system. It is unclear if the current situation will be sustained over time. Four SSA countries are in group 4.

Group 4 countries that address all components of a comprehensive PV system were found to be anglophone countries and have large populations (except for one), viable pharmaceutical markets, and regulatory capacity. The findings suggest that countries with strong regulatory capacity and proactive law enforcement may have improved PV systems performance.

Global Initiatives for Strengthening Pharmacovigilance Systems

A broad range of international and local institutions are working towards strengthening PV and ensuring medicines safety in Africa. There are funding mechanisms available for countries to strengthen their PV systems, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the US President's Emergency Plan for AIDS Relief (PEPFAR), the US President's Malaria Initiative (PMI), Affordable Medicines Facility-malaria (AMFm), and Global Alliance for Vaccines and Immunization (GAVI). Various technical agencies, including WHO, Uppsala Monitoring Centre, the USAID-funded SPS and United States Pharmacopeia/Promoting the Quality of Medicines (USP/PQM) programs, and Medicines for Malaria Venture, provide support to build or improve PV systems. Coordination of these on-going efforts is critical to leverage the limited resources and effectively address the identified gaps in SSA countries' PV systems.

Recommendations for Improvement

The following are summarized recommendations from report—complete recommendations can be found at the end of the report.

PV Components

Policy, Law and Regulation

Countries should develop or revise the relevant policies and legislations to adequately address PV, including regulations for the pharmaceutical industry.

System, Structure, and Stakeholder Coordination

Countries should strengthen organizational structures for PV at all levels of the health system and coordinate PV activities among all stakeholders.

Signal Generation and Data Management

Countries should incorporate active surveillance activities into their national PV systems (either on their own or in collaboration with other countries) and be supported to develop national data warehouses to collate disparate PV data from all sources in the country. Countries should also enhance the use of spontaneous reporting systems for monitoring product quality, medication errors, and treatment failures, and incorporate PV activities into existing surveillance systems.

Risk Assessment and Evaluation

Technical agencies and more advanced regulators can help countries to develop procedures to review, assess, and use relevant global safety reports for local decision making. At the same time, SSA regional communities should be supported to develop regional networks linking researchers and academic institutions in collaboration with regulatory authorities to prioritize and study safety issues of public health importance.

Risk Management and Communication

To improve risk management and communications, countries should be supported to develop framework, tools, and guidance documents for comprehensive risk management practices tailored to local context. They should also develop and implement standardized processes to guide the review and use of safety data.

PV in Public Health Programs

Countries should leverage resources from PHPs for strengthening PV and develop a strategy to use PV data to revise standard treatment guidelines. Countries should be supported to strengthen the collaboration among relevant stakeholders, provide more evidence-based information, and improve communication strategies to address suspicions about vaccine safety.

Patient Safety and PV

Countries should strengthen the capacity of DTCs or other relevant bodies to carry out PV activities and use the data they collect to prevent adverse events and ensure medicine safety at the health-facility level and improve patients' treatment outcomes.

PV in Pharmaceutical Industry

Countries should recognize the pharmaceutical industry as a major stakeholder in PV activities. The industry should replicate PV standard practices that they undertake in developed countries and implement similar activities in SSA countries to safeguard patients and protect the public health of the communities where they market their products.

Support for Strengthening PV Systems

To ensure the sustainability of the national system, donors should develop a plan for gradually transitioning their support to in-country governments and using local resources to support the implementation of medicine safety activities.

Conclusion

The findings of this study demonstrate that PV activities are already taking place in most of the SSA countries. Greater efforts are needed to build this system and to link existing activities to create a comprehensive PV system. Countries should develop strategic plans to incorporate both passive and active approaches, coordinate and work with all stakeholders, strengthen risk management and communication, and enhance the impact of PV and medicine safety systems. These strategic plans should be implemented in a phased approach to meet a country's specific needs and ensure the sustainability of the PV systems. The successful implementation of these plans will improve patient safety and health outcomes.

Introduction

Importance of Medicine Surveillance Systems as Access to Medicines Improves in Africa

The decade-long efforts by international health initiatives, such as the President's Emergency Plan for AIDS Relief (PEPFAR), the President's Malaria Initiative (PMI), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), to provide treatments for HIV/AIDS, TB, and malaria in resource-limited countries has resulted in an increased number of people with access to medicines for the management of these public health diseases. The number of artemisinin-based combination therapy (ACT) treatment courses procured increased from 11.2 million in 2005 to 158 million in 2009.[1] In sub-Saharan Africa (SSA), about 4 million people had access to antiretroviral therapy (ART) in 2009 compared to only 50,000 in 2002.[2] The Global Fund alone has committed 21.9 billion US dollars (USD) to date with 37 percent of funding allocated for health commodities.[3]

With increased access to newly introduced essential medicines, there is a greater need to monitor and promote their safety and effectiveness.

With increased access to newly introduced essential medicines, there is a greater need to monitor and promote their safety and effectiveness. Although many drugs have been used and studied in developed countries, their safety profiles may not necessarily be applicable to other settings, where the incidence, pattern, and severity of adverse drug reactions (ADRs) may differ because of local environmental and genetic influences.[4] Further, scant data on the global burden of ADRs associated with new ACTs and antiretrovirals (ARVs) are available. Thus, the importance of surveillance of medicines-related problems, particularly in Africa with the vulnerable populations receiving treatment for HIV/AIDS, TB, and malaria, is becoming increasingly evident.

The World Health Organization (WHO) had defined PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects

1 World Health Organization (WHO). 2010. World Malaria Report 2010. Available at http://www.who.int/malaria/world_malaria_report_2010/en/index.html

2 WHO. 2010. Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector. Available at http://www.who.int/hiv/pub/2010progressreport/report/en/index.html

3 The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). 2011. Report of the Market Dynamics and Commodities Ad-Hoc Committee to 23rd Board Meeting.

4 Pirmohamed, M., K. N. Atuah, A. N. Dodoo, et al. 2007. Pharmacovigilance in Developing Countries. British Medical Journal 8;335(7618):462.

Poor product quality, ADRs, and medication errors have a huge impact on the health care system.

or any other possible drug-related problems."[5] PV systems should include all entities and resources that protect the public from medicines-related harm, whether in personal health care or public health services. The PV system safeguards the public through efficient and timely identification, collection, and assessment of medicine-related adverse events and by communicating risks and benefits to support decision making about medicines at various levels of the health care system. As yet, few low- and middle-income countries benefit from having a functioning PV system to support medicine safety activities, and countries often lack evidence-based information to help guide treatment decisions and promote rational use—that is, safe, effective, and cost-effective—of medicines.[6] To strengthen the capacity for monitoring safety and effectiveness of medicines in these countries, a comprehensive PV system that collects, evaluates, minimizes, and communicates medicines-related problems must be developed.

Burden of Medicines-Related Adverse Events in Africa

Poor product quality, ADRs, and medication errors have a huge impact on the health care system. ADRs represent the fourth to sixth leading cause of death among hospitalized patients in the United States[7] and, in Europe, it is estimated that 197,000 deaths per year are due to ADRs.[8] The costs of drug-related morbidity and mortality exceeded USD 177 billion in 2000 in the United States[9]; the total estimated annual cost to society due to ADRs in the European Union (EU) is 79 billion euros.[8]

Several studies[10,11,12] documented how ADRs contribute to patient morbidity and hospitalization in Africa—4.5–8.4 percent of all hospital admissions were related to ADRs, 1.5–6.3 percent of patients were admitted as a direct result of ADRs; and 6.3–49.5 percent of all hospitalized patients developed ADRs. Moreover, ADRs accounted for the most frequent reason (45.5 percent) for treatment modification and interruptions in patients on ART. For example, HIV-infected patients receiving ART were more likely to be admitted with an ADR than those not on ART.

Counterfeit medicine is a growing threat across the world, accounting for up to USD 75 billion in sales in 2010.[13] WHO estimates that more than 30 percent of the medicines for sale in some areas in Africa can be counterfeit.[14] In Kenya alone, about USD 65

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7 Lazarou, J., B. Pomeranz, P. Corey. 1998. Incidence of Adverse Drug Reactions in Hospitalised Patients. A Meta-Analysis of Prospective Studies. Journal of the American Medical Association 1998, 279(15):1200-1205

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9 Ernst, F.R. and A. J. Grizzle. 2001. Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model. Journal of the American Pharmaceutical Association 41(2):156-167.

10 Mehta, U., D. N. Durrheim, M. Blockman, et al. 2008. Adverse Drug Reactions in Adult Medical Inpatients in a South African Hospital Serving a Community with a High HIV/AIDS Prevalence: Prospective Observational Study. British Journal of Clinical Pharmacology 65(3):396-406.

11 Tumwikirize, W. A., J. W. Ogwal-Okeng, A. Vernby, et al. 2011. Adverse Drug Reactions in Patients Admitted on Internal Medicine Wards in a District and Regional Hospital in Uganda. African Health Sciences 11(1): 72–78.

12 Jaquet, A., M. M. Djima, P. Coffie, et al. 2011. Pharmacovigilance for Antiretroviral Drugs in Africa: Lessons from a Study in Abidjan, Cote d'Ivoire. Pharmacoepidemiology and Drug Safety: 10.1002/pds.2182

13 WHO. 2010. Bulletin of the World Health Organization: Growing Threat from Counterfeit Medicines. 88:247-248. Available at http://www.who.int/bulletin/volumes/88/4/10-020410/en/index.html

14 WHO. Counterfeit Drugs Kill. May 2008. Available at http://www.who.int/impact/FinalBrochureWHA2008a.pdf

to 130 millions worth of counterfeit medicines are being sold each year.[15] The use of substandard and counterfeit medicines can lead to therapeutic failure, drug resistance, or even death. In Nigeria in 2008, more than 80 children died and many others were hospitalized after being given My Pikin Baby Teething Mixture® a syrup containing a high level of the poisonous solvent diethylene glycol (DEG).[16] In 2005, more than 60,000 people in Niger were inoculated with a counterfeit meningitis vaccine resulting in about 3,000 deaths.[17,18] The extent of morbidity and mortality caused by counterfeit medicines is unknown, since most events are not detected and reported because of weak regulatory systems, lack of enforcement, and the presence of unregulated markets.

Medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of the health care professional, patient, or consumer."[19] The US Institute of Medicine in 2006 estimated that more than 1.5 million Americans are injured every year by medication errors.[20] The analysis of a database in Morocco shows that 14 percent of all suspected ADRs were associated with preventable medication errors.[21]

Insufficient and inadequate resources to monitor safety of medicines; the unreliable supply of quality, safe, and effective medicines; the lack of trained health workers; and the weak state of the health systems in Africa are likely to contribute to significant medicines-related harm.

ADEs have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance

What Happens in the Absence of Functional PV Systems

Some of the data on the burden of adverse drug events (ADEs) mentioned above are from developed countries where PV systems are in existence. When a PV system does not exist at all, the size and magnitude of the problem is completely unknown, but ADEs are still occurring. Besides the impact of ADEs on morbidity and mortality and the attendant costs to health systems, ADEs also have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance. These costs have not been well documented.

What happens when there is no PV system? The following are possible scenarios—

1. Unsafe and poor-quality products are found in the supply chain. WHO estimates that more than 30 percent of the medicines for sale in Africa can be counterfeits.
2. Harm or even death from use of poor-quality products occurs. During the past 70 years, at least 12 occurrences of DEG contamination in oral and topical medications have resulted in more than 700 deaths. These large-

15 US Pharmacopeia (USP). 2011. Media Reports on Medicine Quality. Available at http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/pqm-media-report.pdf

16 British Broadcasting Company. February 6, 2009. Nigeria baby poison deaths rise. Available at http://news.bbc.co.uk/2/hi/africa/7874723.stm

17 WHO. 2006. Nigeria Leads Fight Against "Killer" Counterfeit Drugs. Bulletin of the World Health Organization; 84:690. Available at http://www.who.int/bulletin/volumes/84/9/06-020906/en/index.html

18 International Chamber of Commerce. 1996. Fake Vaccine Leads to 3,000 Deaths in Nigeria. Available at http://www.icc-ccs.co.uk/bascap/article.php?articleid=363

19 National Coordinating Council for Medication Error Reporting and Prevention. 2009. About Medication Error. http://www.nccmerp.org/

20 Aspden, P., J. A. Wolcott, J. L. Bootman, eds. 2007. Preventing Medication Errors. National Academy Press, Institute of Medicine Committee on Identifying and Preventing Medication Errors.

21 Bencheikh, R. S. and G. Benabdallah. 2009. Medication Errors: Pharmacovigilance Centres in Detection and Prevention. British Journal of Clinical Pharmacology 67(6): 687–690.

scale poisonings have occurred predominantly in developing countries and have been associated with inadequate adherence to Good Manufacturing Practices (GMP), lack of enforcement of safe practices, or what appear to be intentionally deceptive drug manufacturing practices. Well-developed and strictly enforced GMP and post-marketing surveillance measures and training programs can prevent such DEG-associated fatal events.

3. Inappropriate uses of medicines abound. WHO estimates that worldwide more than 50 percent of all medicines are prescribed, dispensed, or sold inappropriately, while 50 percent of patients fail to take their medicines correctly.[22]
4. Preventable ADRs occur. It is estimated that over 70 percent of ADRs that resulted in hospitalization are possible or definitely avoidable.[23]
5. Cost of health care delivery escalates. Patients who experienced ADEs were hospitalized an average of 8 to 12 days longer than patients who did not suffer from ADEs, and their hospitalization cost $16,000 to $24,000 more.[24]
6. Patient drop-out and non-adherence increases. Fifty-nine percent of patients concerned about using inhaled corticosteroids (ICS) fear their side effects and 46 percent are reluctant to take ICS on a regular basis.[25] When concerns about side effects are not addressed, they can lead to non-adherence.
7. Therapeutic switches and use of more expensive regimens increases.
8. Resistance to anti-infective medicines occurs.
9. Poor treatment-outcome results and patients die.
10. Patients lose confidence in the health system.

The PV systems framework broadly identifies people, structures, and functions that support national and local decision making and actions to prevent medicine-related problems and ultimately reduce morbidity and mortality.

The above 10 consequences have not been translated into any economic costs. However, it is apparent that they may constitute a profound impact on the resources of the health system. Clearly, there is a need for cost analysis of national PV systems to better understand their value and the return on investment of ensuring an adequate, functioning PV system.

PV Systems Perspective, Framework, and Operational Approach

A comprehensive systems perspective addresses the need for both active and passive approaches to identify medicines-related problems, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of PV activities at all levels of the health system.

The systems perspective aims to address all sources of medicines-related adverse events (figure 1). Adverse events related to medicines may occur because of poor product quality, medication errors (in prescribing, preparing, administering, or taking medicines), or known or unknown pharmacological properties. Adverse events

22 WHO Policy Perspectives on Medicines—Promoting Rational Use of Medicines: Core Components. Available from http://apps.who.int/medicinedocs/pdf/h3011e/h3011e.pdf

23 Pirmohamed, M., S. James, S. Meakin, et al. 2004. Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18,820 Patients. British Medical Journal July 3; 329(7456): 15–19.

24 Agency for Healthcare Research and Quality. Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs. Available from http://www.ahrq.gov/qual/aderia/aderia.htm#ast

25 Boulet, L. P. 1998. Perception of the Role and Potential Side Effects of Inhaled Corticosteroids among Asthmatic Patients. Chest 113:587–592.

resulting from medication errors and quality defects contribute to lack of therapeutic efficacy (treatment failure) and antimicrobial resistance. Many adverse events are predictable and preventable. Identifying and documenting these events is important to protect patients from preventable harm, especially in new products, where the information can result in changes to the medicines' recommended use, product labeling, treatment guidelines, or even a product recall. Therefore, PV systems should monitor events that may be related to product quality, medication errors, treatment failure, and previously known or unknown ADRs.

The PV systems framework (figure 2) broadly identifies people, structures, and functions that support national and local decision making and actions to prevent medicine-related problems and ultimately reduce morbidity and mortality. The systems perspective highlights the need for building capacity to carry out both passive and active methods for generation of signals and evaluation, quantification, and identification of risk factors. The passive approach includes spontaneous reporting by health care providers and patients; this helps identify unexpected and rare adverse events; this is most frequently used to detect medicine safety issues. The active approach involves searching for exposures or events at sentinel sites and following up patients who have been exposed to medicines of interest; this also allows obtaining a denominator to calculate adverse event rates. These approaches complement each other and ensure a robust and comprehensive system for addressing medicine safety issues. As the PV system matures, it may expand from a program based strictly on passive ADR surveillance to a system that incorporates active surveillance methods, such as the use of registries, sentinel sites, and follow-up of a defined patient cohort, to address priority safety concerns.

Figure 1. Sources of medicines-related adverse events

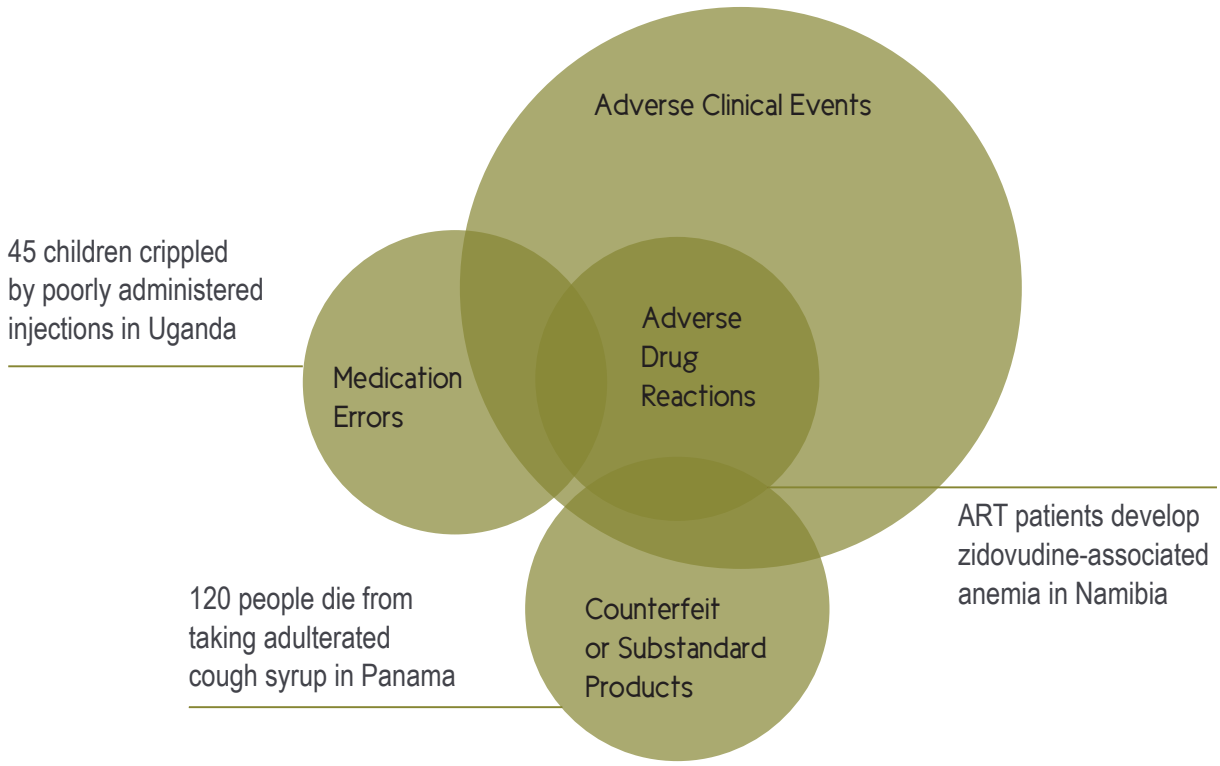
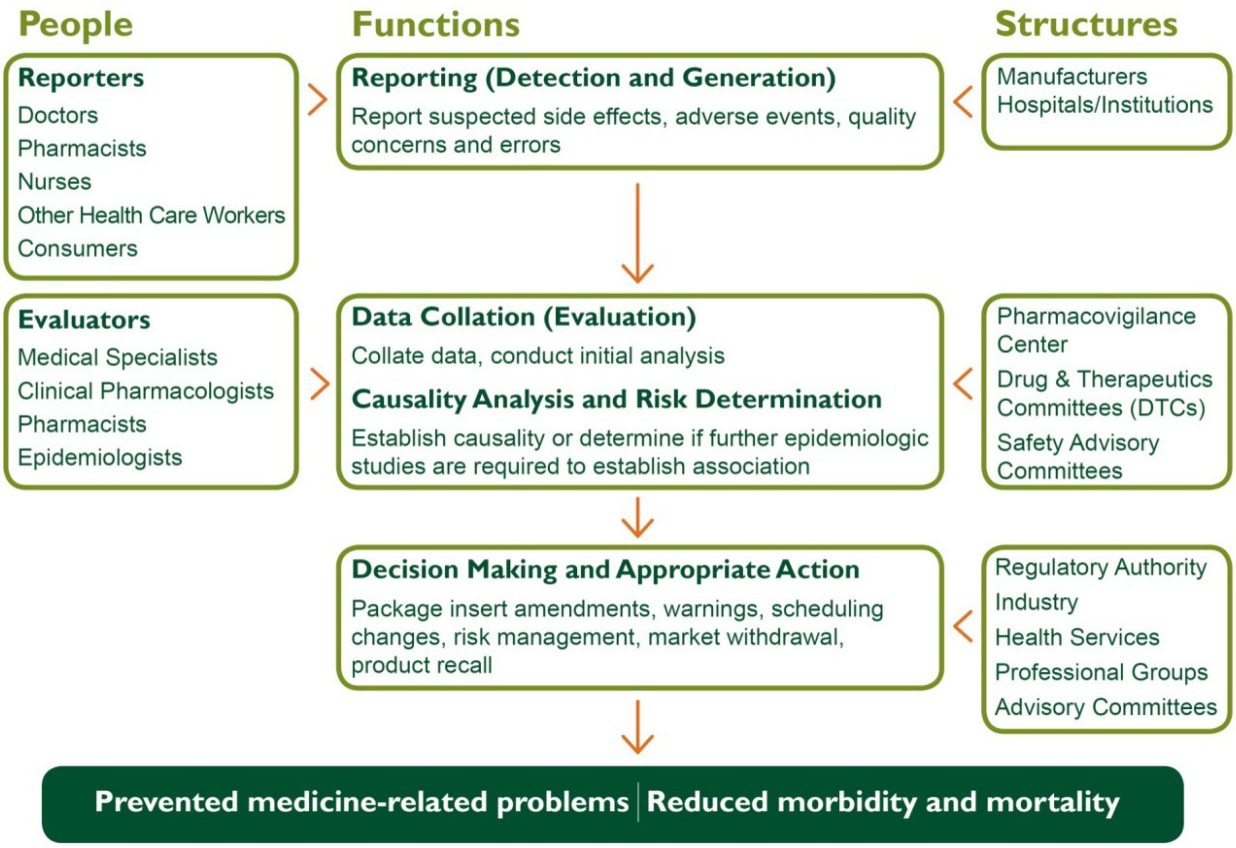


Figure 2. PV framework



Source: Center for Pharmaceutical Management. 2011. *Center for Pharmaceutical Management: Technical Frameworks, Approaches, and Results*. Arlington, VA: Management Sciences for Health.

Global Standards for Functioning PV

Before beginning a discussion of PV standards in SSA, it is important to understand what PV standards are in other parts of the world. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) provides standard guidelines and processes for national medicines regulatory authorities (NMRAs) and the pharmaceutical industry to register products. In particular, the ICH guidelines E2A to E2F (table 1) cover reporting and evaluating the data on safety and efficacy of pharmaceutical products in pre- and post-approval periods.[26] The topics include clinical safety data management for expedited reporting, individual case safety reports, periodic safety update reports (PSURs), post-approval safety data management, PV planning for industry, and development safety update reports from clinical trials.

These international guidelines are adopted by stringent regulatory authorities (SRAs) such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Standardization and harmonization of the processes offers benefits as they prevent duplication of effort, enhance information sharing, minimize risk to public health, and reduce the times and resources for medicines development

26 The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Efficacy Guidelines. Available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

Table 1. ICH Guidelines

ICH Guidelines
E2A (definitions and standards for expedited reporting)
Provides standard definitions and terminology for key aspects of clinical safety reporting and guidance on handling expedited reporting of ADRs in drug development
E2B (maintenance of the clinical safety data management including data elements for transmission of individual case safety reports)
Defines the data elements for the transmission of all types of individual case safety reports for both pre- and post-approval periods and covers both ADR reports and adverse event reports
E2C (periodic safety update reports for marketed drugs)
Provides guidance on the format and content of safety updates to be provided at intervals to regulatory authorities on registered medicines
E2D (definitions and standards for expedited reporting on post-approval safety data)
Sets out a standardized process for expedited reporting to regulatory authorities of post-approval safety data obtained from consumers, literature, and Internet
E2E (pharmacovigilance planning)
Identifies safety specification and PV activities for the early post-marketing period of a new drug
E2F (development safety update report)
Provides guidance on managing data from interventional clinical trials for both pre- and post-approval periods

Source: ICH website, available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

and evaluation. Those benefits also apply to the regulatory authorities and PHPs in resource-limited settings where newly developed medicines are available.

FDA Medicines Safety System

In the United States, the reporting of adverse events is mandated by the Federal Food, Drug, and Cosmetic Act Sub-Chapter H Section 760 and 761. The regulations governing drug safety are covered by Title 21 of the Code of Federal Regulations.[27] Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007 provided FDA with enhanced authorities regarding post-market safety of drugs including statutory powers to demand post-authorization safety studies.

The FDA's Drug Safety Oversight Board mandated by the FDAAA advises on how to handle and communicate important and emerging drug safety issues. The Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, is responsible for post-marketing PV, pharmacoepidemiology, risk management, and medication error prevention and analysis. FDA implements the MedWatch program,[28] which provides clinically important safety information and a mechanism to report serious problems with human medical products. Through MedWatch, health professionals and consumers can voluntarily report serious adverse events (SAEs), product quality problems, medication errors, and therapeutic failure by submitting the FDA 3500 reporting form online. Importers, distributors, and manufacturers can report through the FDA 3500A mandatory reporting form.

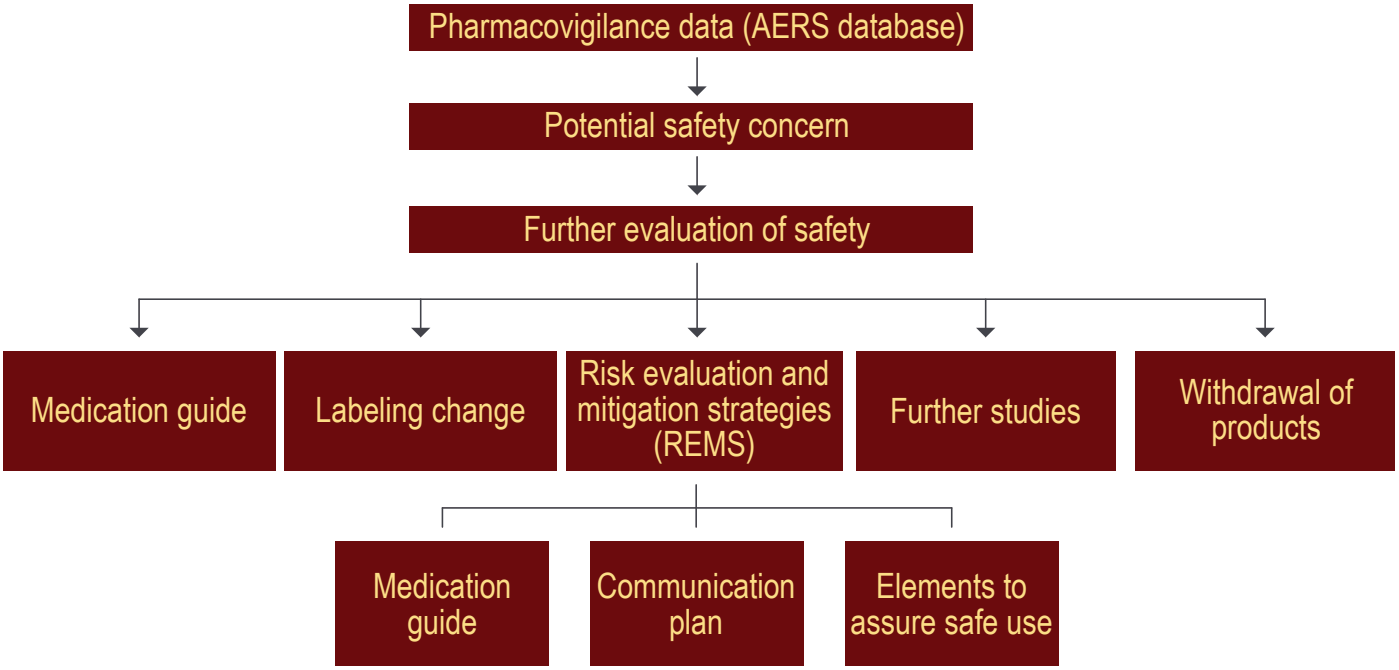
27 Sections of 21 CFR addressing safety reporting include 310.305, 314.80, 314.81, 314.90, 314.98, 314.99, 314.540, and 314.630.

28 US Food and Drug Administration (FDA). Medwatch: The FDA Safety Information and Adverse Event Reporting Program. Available at http://www.fda.gov/Safety/MedWatch/default.htm

The database for the spontaneous reports is the Adverse Event Reporting System (AERS)[29] and its structure is in compliance with international safety reporting guidance (ICH E2B).[30] The AERS database was designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. Adverse events in AERS are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The AERS database contains over four million records as of December 31, 2010.[31] The FDA, in collaboration with the US Centers for Disease Control and Prevention, also administers the Vaccine Adverse Event Reporting System (VAERS) which is the national vaccine safety surveillance program collecting information about adverse events that occur after vaccines are given. FDA posts AERS statistics on the website quarterly. In addition, quarterly reports containing selected fields of information are released on the web, so that individual cases can be reviewed, though not all information in the report is in this quarterly report. The VAERS data can be obtained either by sending a freedom of information request to FDA or searching the online database.[32]

With regards to active surveillance, based on the FDAAA Section 905 mandate, the FDA developed the Sentinel Initiative as an electronic proactive system to monitor post-market performance of medical products by accessing existing automated health care data sources

Figure 3. FDA process of medicine safety data



29 FDA. Adverse Event Reporting System. Available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

30 International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2001. Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports E2B. available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2B/Step4/E2B_R2__Guideline.pdf

31 FDA Adverse Events Reporting System. Available from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm

32 http://vaers.hhs.gov/data/data

such as insurance claims databases, electronic health records, and registries.[33] Figure 3 illustrates how the FDA processes drug safety data once a potential safety concern is identified in the AERS database. It is important to note that a Medication Guide can be required or updated with or without risk evaluation and mitigation strategies.

European Medicines Agency Medicine Safety System

The European Parliament and European Council adopted EU regulation No 1235/2010[34] and Directive 2010/84/EU[35] in 2010 that will govern PV systems in regulatory authorities in EU member states and pharmaceutical companies. Volume 9A of the Rules Governing Medicinal Products in the EU provides PV guidelines for MAHs, regulatory authorities, electronic exchange of PV in the EU, and PV communication.[36]

The regulatory PV system of the EU comprises the member states' competent authorities, the European Commission as the competent authority for medicinal products authorized centrally in the EU, and EMA with responsibilities for coordinating PV systems in the EU. The EMA's Pharmacovigilance Working Party makes recommendations on the safety of medicines and the investigation of ADRs associated with medicines on the EU market to the Committee for Medicinal Products for Human Use (CHMP).[37] CHMP is responsible for conducting both pre- and post-authorization assessments of medicines in the EU.

The EMA's Pharmacovigilance and Risk Management Sector manages Eudravigilance, a central database containing case reports received from over 40 regulatory agencies in member states and pharmaceutical companies. Volume 9A requires that all adverse events in the database be coded in MedDRA terminology, which is in accordance with the ICH E2B guideline. It also provides additional reporting requirements in special situations including adverse reactions during breastfeeding, use of medicinal products in children, medication errors, overdose, abuse and misuse, and lack of efficacy. Currently, MAHs submit ADR reports and PSURs via national regulatory authority. With the implementation of the new regulation, MAHs will be able to submit the reports directly to EMA's electronic database.

The EMA established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) in 2006 to facilitate the conduct of independent, multi-center, post-authorization studies focusing on safety and risk-benefit.[38] This network comprises EU research institutions, databases, and registries covering rare diseases, therapeutic fields, and adverse events of interest. The EnCePP Database of Research Resource provides an inventory of research centers and networks and the registry of EU data sources. In 2010, it also launched the E-Register, which provides a publicly accessible resource for the registration of pharmacoepidemiological and PV studies.

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33 FDA's Sentinel Initiative. Available from http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm

34 Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF

35 Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF

36 The European Commission. 2008. Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf

37 EMA. 2005. Mandate, Objective and Rules of Procedure for the CHMP Pharmacovigilance Working Party. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500073703.pdf

38 The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website. Available at http://www.encepp.eu/events/index.html

Information regarding new safety concerns, particularly those resulting in major changes to the marketing authorization status, revocation, or withdrawal of a product, is exchanged between the member states, the EMA, and the European Commission through EU rapid alert and incident management systems. A rapid alert is circulated for those requiring urgent action to protect public health (e.g., when a member state suspends the marketing and use of medicinal products) within one day. The rapid alert system is also used to send notifications concerning medicine quality defect or counterfeits.[39]

To ensure that the benefits of medicines exceed the risks, the EMA has a risk management system complying with the ICH-E2E guideline that requires MAHs to submit an EU risk management plan (RMP) for all newly authorized medicines. It should contain the safety specification, a PV plan, an evaluation of the need for risk minimization activities, and, if there is a need for additional risk minimization activities, a risk minimization plan.[34,36]

Assessing PV Systems and Their Performance in SSA

The Strengthening Pharmaceutical Systems (SPS) Program conducted a study in 2011 to assess the current state of PV systems and their performance in SSA and to recommend options to address identified gaps and further enhance existing systems. This assessment, performed under an interagency agreement between the FDA and the US Agency for International Development (USAID), complemented previous efforts and provides additional values in—

- Benchmarking PV system capacity and performance
- Comparing performances with the pharmaceutical profiles of countries
- Encouraging countries to use data from the assessment to develop plans for medicine safety systems improvement

Assessment Objectives

- Provide a comprehensive description and analysis of national PV systems in selected African countries with a specific focus on capacity and performance
- Identify replicable and successful experiences to further enhance PV systems and classify countries based on performance
- Map out how donor agencies and global health efforts are contributing to PV and analyze the strategies employed by global and regional initiatives supporting PV in Africa
- Recommend options for enhancing PV system capacity and performance

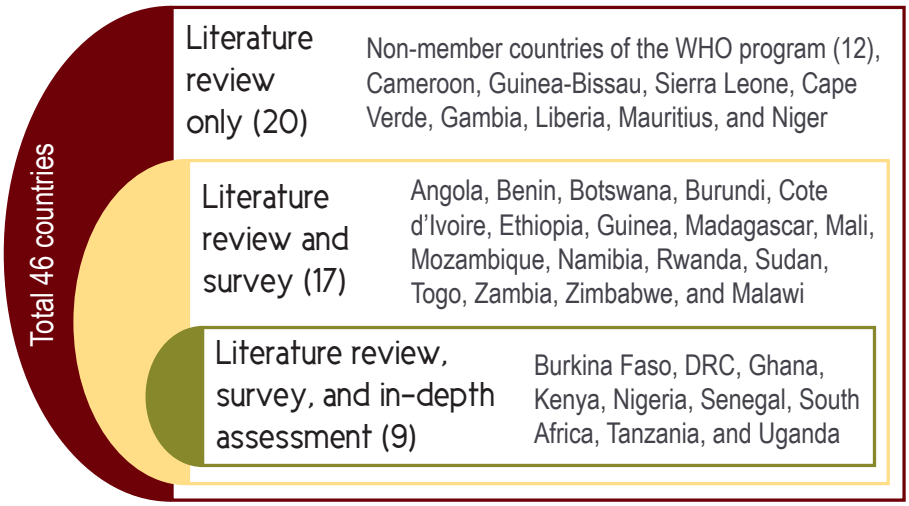
Methods

We compiled data from various sources to conduct this study (figure 4). Relevant literature from MEDLINE, scientific journals, national regulatory authorities' websites, Global Fund proposals, donors' websites, the SPS PV conference in 2010, the WHO website, and the clinical trial registration website[40] were reviewed to determine to what extent PV activities

39 EMA. 2011. Compilation of Community Procedures on Inspections and Exchange of Information. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004706.pdf

40 http://clinicaltrials.gov/ It is a registry and database of federally and privately supported clinical trials conducted in the US and around the world.

Figure 4. Study method



are conducted in SSA and to map out the contributions and involvement of technical/advocacy and financing institutions. The search terms and keywords included "adverse drug reaction/adverse event/side effect monitoring" OR "adverse events following immunization (AEFI)" OR "pharmacovigilance" OR "pharmacoepidemiology" OR "drug or medicine safety" OR "post marketing surveillance" AND "Africa."

To supplement the data obtained from published articles in the literature, we reviewed recent reports and publications and consulted opinion leaders to identify the key literature on recent developments in drug regulation in Africa. Based on the recommendations, we reviewed the following reports: the WHO country pharmaceutical profiles,[41] World Medicines Situation Reports 2004 and 2011,[42,43] WHO assessment of medicines regulatory systems 2002 and 2010,[44,45] the Business of Health in Africa,[46] Strengthening Pharmaceutical Innovation in Africa,[47] the African Network for Drugs and Diagnostics Discovery and Innovation,[48] African Medicines Registration Harmonisation Initiative,[49] and World Health Statistics 2010.[50] These documents helped to explain the broader context of PV within the health system and to identify contributing factors.

41 WHO. Pharmaceutical Sector Country Profiles. Available at http://www.who.int/medicines/areas/coordination/coordination_assessment/en/index2.html

42 WHO. 2004. The World Medicines Situation. Available at http://apps.who.int/medicinedocs/en/d/Js6160e/

43 WHO. 2011. The World Medicines Situation Report. Available at http://www.who.int/medicines/areas/policy/world_medicines_situation/en/index.html

44 WHO. Effective Drug Regulation – A Multicountry Study and Annex 1: Guide for Data Collection to Assess Drug Regulatory Performance. Available at http://apps.who.int/medicinedocs/en/d/Js2300e/

45 WHO. 2010. Assessment of Medicines Regulatory Systems in Sub-Saharan African Countries. An Overview of Findings from 26 Assessment Reports. Available at http://apps.who.int/medicinedocs/en/m/abstract/Js17577en/

46 International Finance Corporation (IFC). 2007. The Business of Health in Africa: Partnering with the Private Sector to Improve People's Lives. Washington, DC: IFC. Available at http://www.ifc.org/ifcext/healthinafrica.nsf/AttachmentsByTitle/IFC_HealthinAfrica_Final/$FILE/IFC_HealthinAfrica_Final.pdf

47 Berger, M; Murugi, J; Buch, E; IJsselmuiden C; Kennedy, A; Moran, M; Guzman, J; Devlin, M; Kubata, B. Strengthening pharmaceutical innovation in Africa. Council on Health Research for Development (COHRED); New Partnership for Africa's Development (NEPAD) 2009. Available at http://www.policycures.org/downloads/COHRED-NEPAD_Strengthening_Pharmaceutical_Innovation_AfricaREPORT.pdf

48 The African Network for Drugs and Diagnostics Innovation website. Available at http://www.andi-africa.org/

49 African Medicines Registration Harmonisation website. Available at http://amrh.org/documents/index.php

50 WHO. 2010. World Health Statistics. Available at http://www.who.int/whosis/whostat/2010/en/index.html

To fill gaps in data from existing sources, a survey was sent to 29 country members of the WHO Programme for International Drug Monitoring[51] in June 2011 to which 26 countries responded.[52] Nonmember countries were excluded as it is likely that there would be minimal or no activity related to PV.

We also collected data through in-depth assessments in nine countries—Burkina Faso,[53] the Democratic Republic of the Congo (DRC), Ghana, Kenya, Nigeria, Senegal, South Africa,[54] Tanzania, and Uganda from May to August 2011. The criteria used to select countries for in-depth assessment were geography, language, involvement in global public health initiatives (i.e., PEPFAR, PMI, and the Global Fund), pharmaceutical manufacturing capacity, and the size of the pharmaceutical sector. Other selection criteria included the existence of WHO prequalified quality control laboratories, use of active approaches to PV, membership in the WHO Programme for International Drug Monitoring, and existence of an NMRA. The data collection tool was adapted from the indicator-based pharmacovigilance assessment tool (IPAT)[55] for in-country assessment. We collected data at national, PHP, and health-facility levels by interviewing various stakeholders, such as the Ministry of Health, the NMRA, the national PV center/unit/department, the drug information center, pharmaceutical industry, universities conducting medicines safety research or collaborating with the national PV center, other relevant professional associations or institutions, key PHPs (including national HIV/AIDS, TB, malaria, and immunization programs), and Drug and Therapeutic Committees (DTCs) in hospitals.

In total, this study includes data for 46 countries in SSA. Therefore, the denominator for many of the statistics given is 46, unless otherwise noted. Data for all countries can be found in annex A. It should be noted that when a country is counted as not having a particular regulatory feature, it could mean that either the country does not have that particular feature or that information on the feature could not be obtained.

51 Survey was sent to the members of the WHO Programme for International Drug Monitoring as of May 2011. Later in 2011, five more countries became associate members (Cape Verde, the Gambia, Liberia, Mauritius, and Niger) which are not included in survey. Source: the Uppsala Monitoring Centre website (last updated on August 18, 2011). Available at http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442

52 Cameroon, Guinea-Bissau, and Sierra Leone didn't respond to the survey.

53 Burkina Faso was not selected for in-depth assessment initially, but added because of availability of data collector.

54 In South Africa, the in-depth assessment was conducted in the pharmaceutical industry only at the time of this study. An assessment in the public sector is underway.

55 Strengthening Pharmaceutical Systems (SPS) Program. 2009. Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. Available from http://pdf.usaid.gov/pdf_docs/PNADS167.pdf

Current State of Pharmacovigilance Systems in Africa

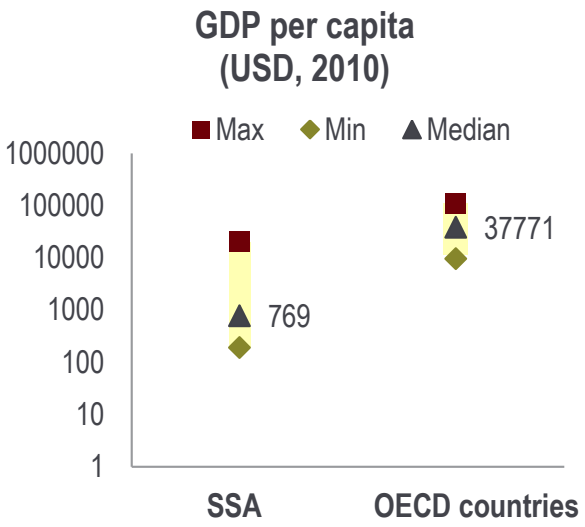
SSA Pharmaceutical Profile

More than 800 million people live in 46 SSA countries, accounting for about 11 percent of the total global population. Limited resources in SSA are reflected in very low gross domestic product (GDP), expenditures on health, expenditures on medicines, and health workforce compared to other developed countries. Health coverage, defined as the population formally covered by social health protection (e.g., under legislation, without reference being made to effective health services, quality of services, or other dimensions of coverage), is less than 10 percent in more than half of SSA countries. Figure 5 below shows a number of demographic characteristics of the SSA region, including GDP per capita, total expenditure on health per capita, total pharmaceutical expenditure (TPE) per capita, health workforce per population, and health coverage in 2008, compared to Organisation of Economic Co-operation and Development (OECD) and other high-income countries. For example, the TPE per capita represents the total consumption of pharmaceuticals, regardless of the means of distribution, the place or condition of consumption, or its type. According to the WHO report which used 2005/2006 data, the TPE is determined by price and quantity of medicines purchased and ranged from USD 7.61 in low-income countries to USD 431.6 in high-income countries. On the health workforce per population chart, health workforce is defined as total number of physicians, nurses and midwives, dental personnel, pharmaceutical personnel, public health workers, and community health workers. The WHO report notes that the data may have underestimated or overestimated the actual size of the health workforce due to double counting of health workers holding two or more jobs at different locations and other factors. The 2008 health coverage data from the Rockefeller Foundation represents the population formally covered by social health protection.

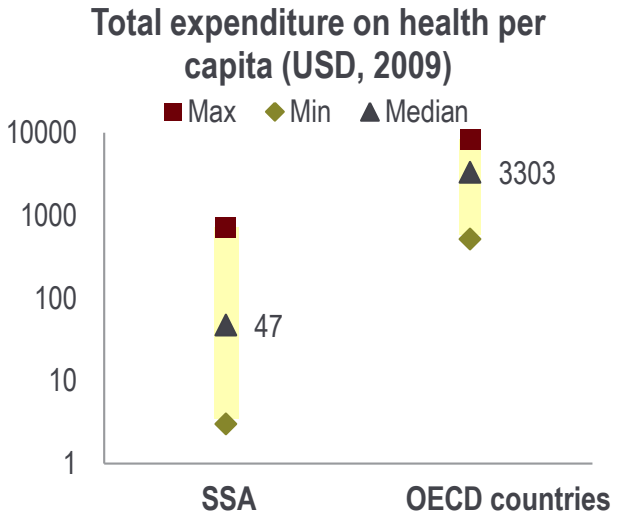
Africa remains the region with the highest burden of malaria and HIV/AIDS—25 million people living with HIV/AIDS resided in SSA in 2009, representing 68 percent of the global HIV burden.[56] For malaria, 78 percent of worldwide cases and 91percent

56 UNAID. Factsheet: sub-Saharan Africa. 2010. Available at http://www.unaids.org/en/media/unaids/contentassets/documents/factsheet/2010/20101123_FS_SSA_em_en.pdf

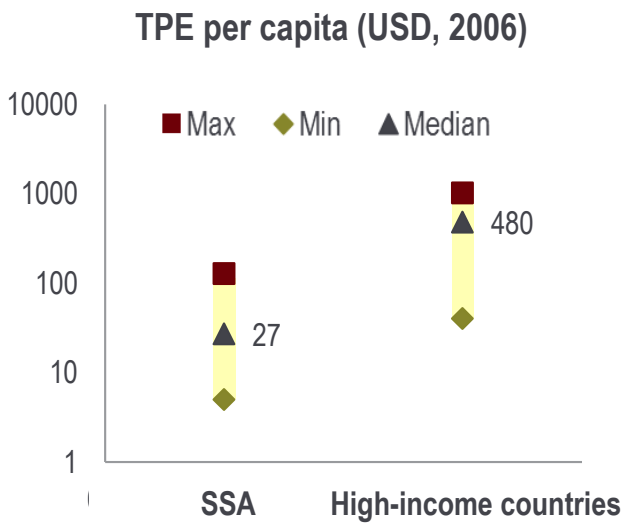
Figure 5. Health development in SSA



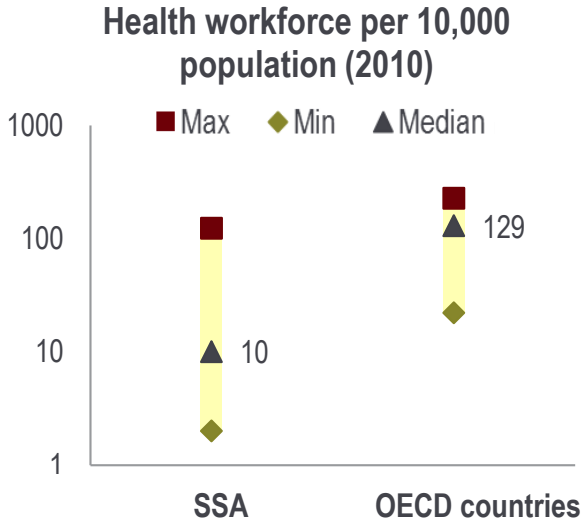
Source: World Bank, 2010



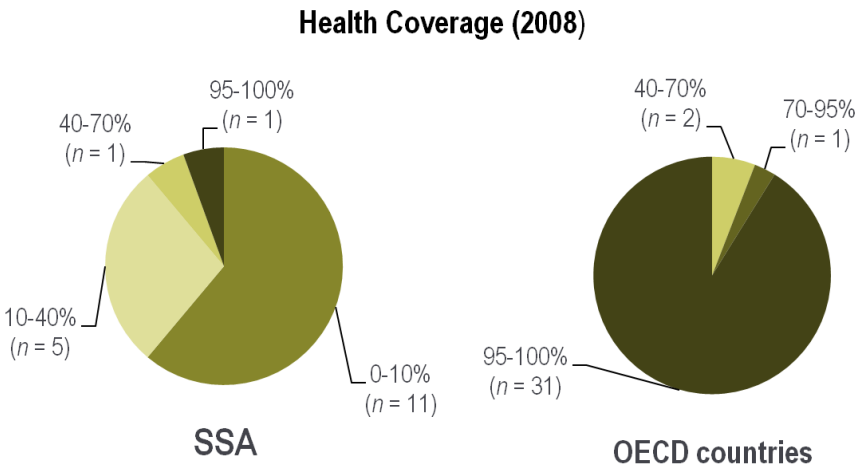
Source: WHO national health account database, 2009



Source: WHO, World Medicines Situation, 2010



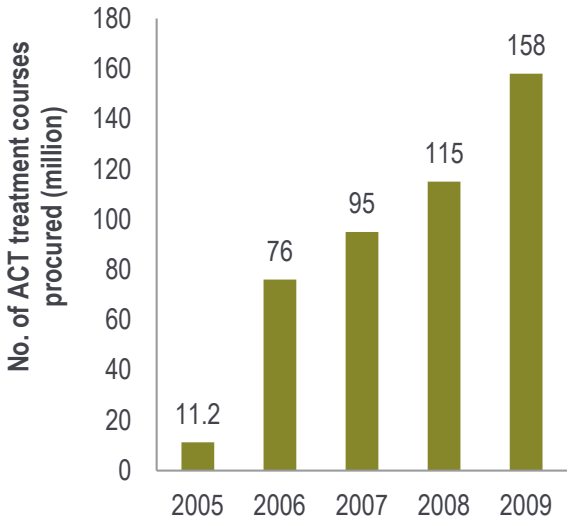
Source: WHO world health statistics 2011, WHOSIS. Note: Data for health workforce is total number of physicians, nursing and midwifery personnel, dentistry personnel, pharmaceutical personnel, public health workers, and community health workers.



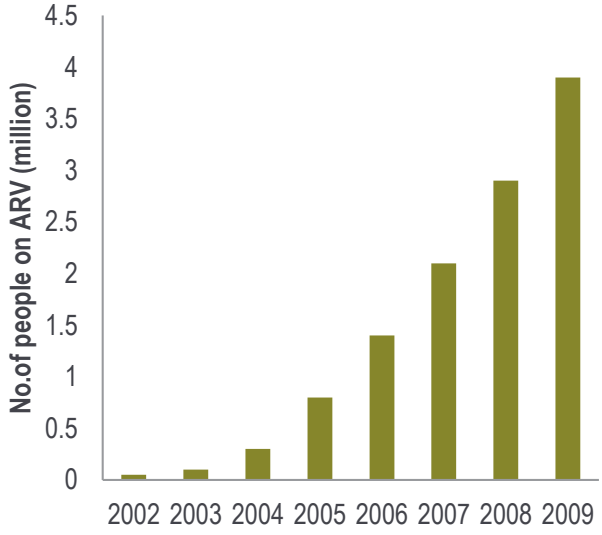
of deaths occurred in the region in 2009.[57] In addition, 9 of the 22 countries with the highest burden of TB are SSA countries.[58] However, SSA countries now have increased access to medicines to combat these diseases because of various global initiatives. Figure 6 shows two examples of this trend toward increasing access to medicines over time, including the number of ACT courses procured and the number of people on ARVs.

With an estimated pharmaceutical market size of between USD 3.8 billion to 4.7 billion and some local manufacturing capacity in 80 percent of SSA,[46,59] medicines regulatory capacity in many of these countries is inadequate.[45] Of the 46 SSA countries, only 74 percent have a NMRA, 78 percent have a national medicines policy (NMP), and 41 percent of NMRAs have a website. As of May 2011, there are only 5 WHO prequalified quality control laboratories in SSA (2 in South Africa, 2 in Kenya, and 1 in Tanzania), and 1 WHO prequalified manufacturing facility in Uganda (figure 7).[60,61] Figure 7 also shows the number of registered drugs in a country by the number of countries. Most countries have between 2001 and 4000 drugs registered with their regulatory authorities. Efforts at strengthening medicines registration need to be matched by equally strong post-marketing surveillance activities. The registration of a medicine should not be an end in itself. The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug;

Figure 6. Increased access to medicine in SSA



Source: WHO, World Malaria Report, 2010



Source: WHO, Toward universal access: scaling up priority HIV/AIDS interventions in the health sector; 2008-2010

57 WHO. 2010. World Malaria Report. Available at http://www.who.int/malaria/publications/atoz/9789241564106/en/

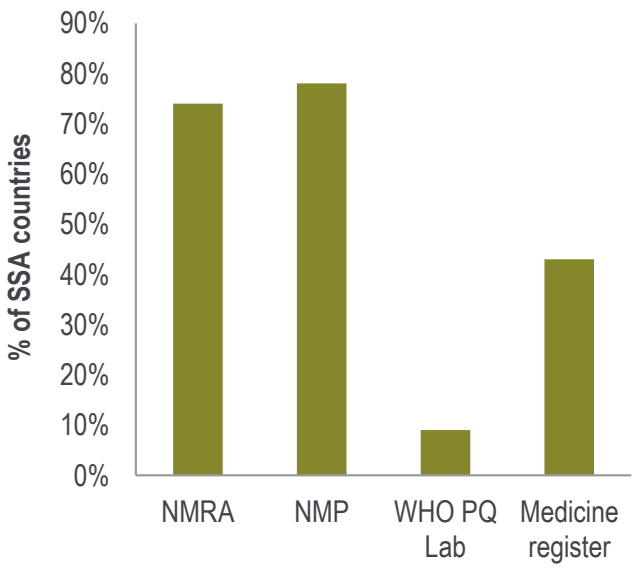
58 WHO. 2010. Global Tuberculosis Control. Available at http://www.who.int/tb/publications/global_report/2010/en/

59 United Nations Statistics Division (UNSD). Commodity Trade Statistics Database: Pharmaceutical Products 2006.

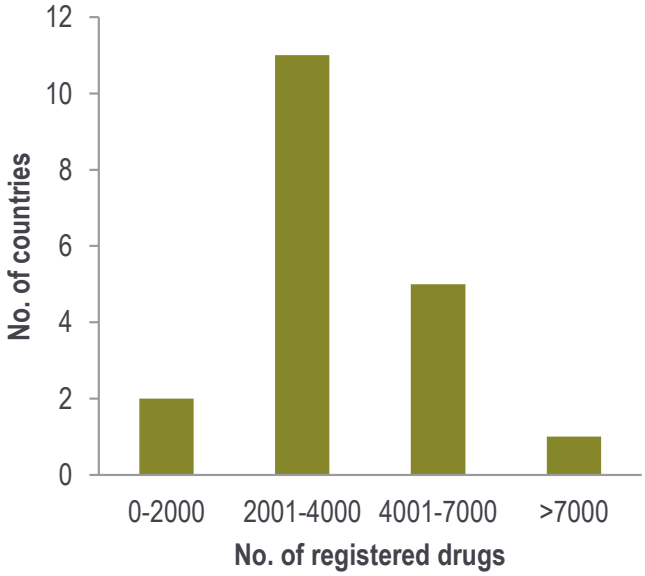
60 WHO. List of prequalified quality control laboratories. 20th ed. October 2011. Available at: http://apps.who.int/prequal/lists/PQ_QCLabsList.pdf

61 Anderson, T. 2010. Tide Turns for Drug Manufacturing in Africa. The Lancet, May 8; 375 (9726):1597-1598. Available at http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60687-3/fulltext

Figure 7. Pharmaceutical profile in SSA



Source: multiple sources including interview, WHO pharmaceutical profile, national regulatory authorities website, and WHO list of prequalified quality control laboratories, May 2011



Source: WHO pharmaceutical profile, national regulatory authority website

preapproval clinical trials do not obviate continuing formal evaluation after approval.[62] Therefore, as many SSA countries increase the number of products in their national medicines register, PV activities should equally be strengthened.

Although counterfeit medicines and poor-quality medicines are circulating in Africa,[63] only 20 percent of countries are testing samples for post-marketing surveillance. New initiatives have emerged, including the African Medicines Registration Harmonisation (AMRH) Initiative, aimed at ensuring rapid access to safe, efficacious, and good quality essential medicines by reducing the time to register medicines for the treatment of priority diseases. Such initiatives strive to strengthen regulatory capacity and systems and better coordinate the registration process in Africa, which can serve as an entry point to broaden the scope to other regulatory functions and products. As products become available and accessible in the market through improved registration, the safety, quality, and effectiveness of products should be continuously monitored and, therefore, AMRH and related initiatives need to incorporate PV into the process of strengthening regulatory capacity and systems. The AMRH initiative works through the African regional economic communities (RECs)—Southern African Development Community (SADC), Economic Community of West African States (ECOWAS), East African Community (EAC), and Economic Community of Central African States

62 National Research Council. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press, 2007.

63 USP, Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda, Nov 2009, available at http://www.usaid.gov/our_work/global_health/hs/publications/qamsa_report_1109.pdf

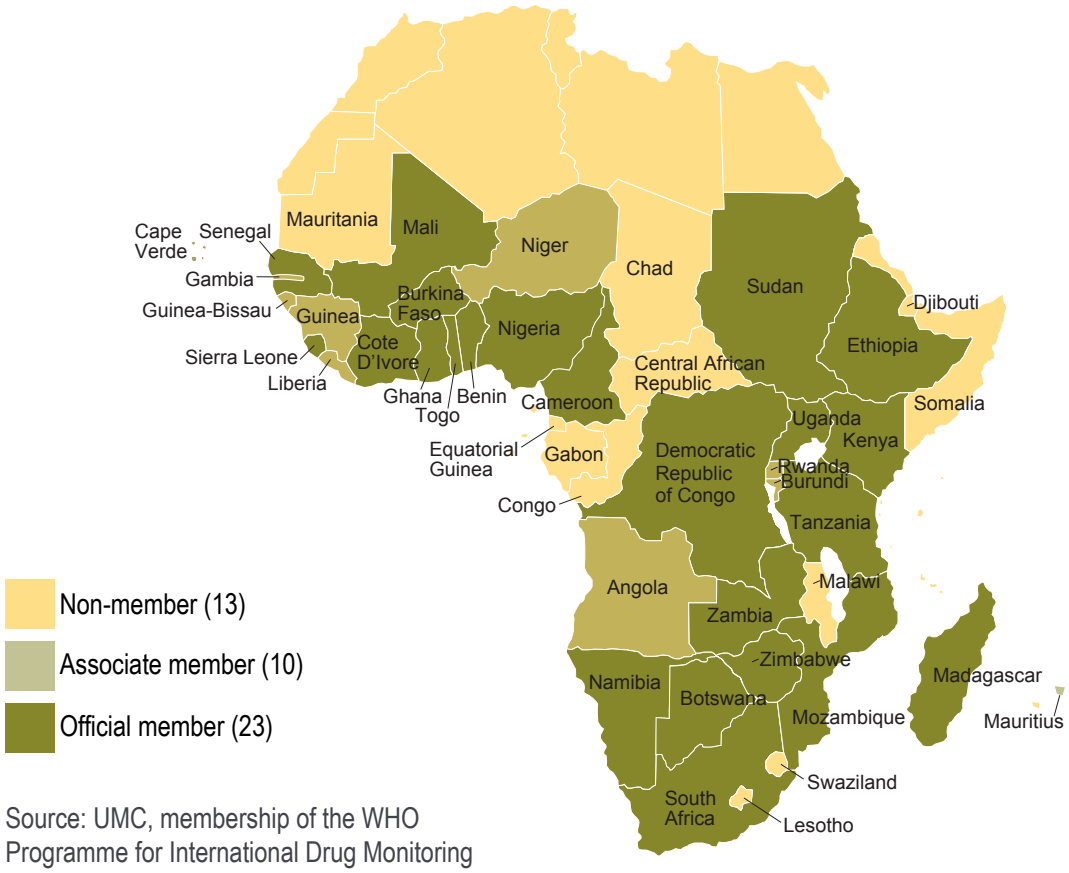
(EECAS).[64] There are 23 official members and 10 associate members[65] of the WHO international drug monitoring program in SSA, and most of them (except South Africa [1992], Tanzania [1993], and Zimbabwe [1998]) became members after 2000 (figure 8).

Components of PV

Policy, Law, and Regulation

Existence of a policy containing essential statements on PV indicates that a country has demonstrated its high-level commitment to improve medicine safety and quality and helps to provide a broad direction to advance the system. Similarly, existence of laws and regulations provides a firm legal basis to ensure compliance by relevant parties and stakeholders. WHO recommends that key elements of PV should be included in the NMP and legislation/regulations need to be developed for medicine

Figure 8. WHO Programme for International Drug Monitoring members in SSA



Source: UMC, membership of the WHO Programme for International Drug Monitoring

Note: Sudan includes both Sudan and South Sudan.
The source data was last updated on August 18, 2011.

64 African Medicines Registration Harmonisation Initiative: Summary, Status and Future Plans. Nov. 2009. Available at http://amrh.org/download/eng_amrh_workshop_ssfp.pdf

65 Once a country submits a formal application to be admitted as a member of the WHO Drug Monitoring Programme, it becomes an associate member. The basic requirements to join the WHO program are existence of a spontaneous reporting system, existence of a national center for drug monitoring designated by the Ministry of Health, and a capacity to submit case reports. Once technical capability to submit data is verified with a sample of at least 20 reports, the country becomes an official member of the WHO program.

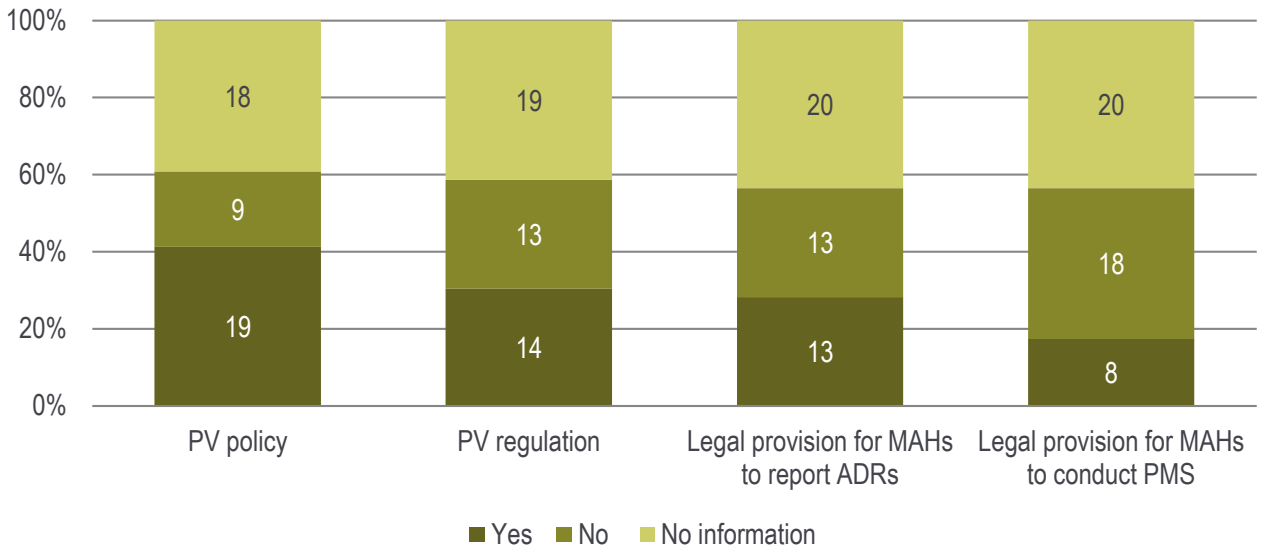
The lack of relevant policy and regulations reflects fundamental limitations for enforcing medicine safety monitoring.

monitoring.[66] Although NMP exists in 78 percent of SSA, national policy related to PV or medicine safety exists in only 19 countries (41 percent) and mostly as a part of NMP. There are 14 countries (30 percent) with laws and regulations that provide a legal mandate for PV and medicine safety activities. Regulations to enforce the pharmaceutical industry responsibilities are lacking in most countries; only 13 (28 percent) and 8 (17 percent) countries have legal provisions that require MAHs to mandatorily report all serious ADRs to their NMRAs and conduct post-marketing surveillance activities, respectively (figure 9).

The lack of relevant policy and regulations reflects fundamental limitations for enforcing medicine safety monitoring. For example, the lack of a legal framework for PV in Burkina Faso, Ghana, and Uganda (which are countries with sizeable pharmaceutical industries in the African context) limited the capacity of the regulatory authorities to enforce the responsibilities of the MAH for product stewardship. Almost none of the pharmaceutical companies in these countries were committed to post-marketing safety activities. (See additional details in PV in Pharmaceutical Industry on page 70.)

Although there might be general statements related to the responsibilities of regulatory authorities for ensuring medicine efficacy, safety, and quality, most policy statements are not specific or comprehensive enough to address the need, scope, direction, and activities a country should carry out at all levels of the health system. The analysis of policies and regulations (table 2) in the selected countries shows to what extent medicine safety and PV are addressed. Nigeria has drafted a policy that covers broad aspects of PV[67] in addition to the national drug policy.[68] The PV policy will provide a sound framework to further strengthen a national PV system, once approved. (See additional details on Nigeria under PV systems in selected countries on page 100.)

Figure 9. Policy, law, and regulation



66 WHO. 2004. Pharmacovigilance: Ensuring the Safe Use of Medicines. WHO Policy Perspective on Medicines 9. http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf

67 NAFDAC. Draft Nigerian National Pharmacovigilance Policy and Implementation Framework. 2011

68 Federal Ministry of Health, Nigeria. National Drug Policy. 2005

Table 2. National PV Policy and Regulation

Country	Essential component of PV policy and regulation							
	PV policy	PV law or regulation	Need for monitoring adverse events	Establishment of national PV center	Scope of PV[a]	Both passive and active approaches	Roles and responsibilities of stakeholders	Information sharing
Burkina Faso	■		■	■	■	■		■
DRC	■		■	■				
Ghana	■		■	■		■		■
Kenya[b]		■	■					
Nigeria	■[c]	■[d]	■	■	■	■	■	■
Senegal	■	■	■	■	■		■	■
Tanzania[e]		■	■	■				■
Uganda	■		■					

[a]ADRs, product quality, medication errors, and treatment failure
[b]Draft national pharmaceutical policy 2010
[c]NMP 2005 and draft Nigerian national pharmacovigilance policy and implementation framework 2011
[d]NAFDAC act 1993 and draft good pharmacovigilance practice regulation 2009
[e]Draft national medicine policy is waiting for approval

System, Structure, and Stakeholder Coordination

The development of sustainable structures and their optimal functioning are critical to PV systems. Several surveys documented that PV activities are not well integrated into regulatory functions and structures of NMRAs or other PHPs in countries.[69] Lack of sufficient funding, infrastructure, trained staff, and training programs on medicines risk management in pre- and post-service education were also identified as major constraints in previous surveys.[70,71,72]

In Africa, at least 34 countries (74 percent)[73] have a PV center or unit with a clear mandate and formal organizational structure. They are usually affiliated with the Ministry of Health or NMRA and 76 percent of PV centers generally have funding available from government and donor organizations. Drug information services are provided in 22 countries (48 percent). Drug information service is provided by the PV center in 14 countries and by another unit, department, or institutions outside of the PV unit in 8 countries. Where drug information service is provided separately, establishing a linkage between the PV center and such a unit providing drug information service is important to ensure the optimal use of the service; for

69 Olsson, S., S. N. Pal, A. Stergachis, et al. 2010. Pharmacovigilance Activities in 55 Low- and Middle-Income Countries: A Questionnaire-Based Analysis. Drug Safety 33(8):689-703.
70 Lalvani, P. S. 2007. Situation Analysis of the Pharmacovigilance Capacity of Kenya, Tanzania and Uganda. RaPID Pharmacovigilance. Available at: http://www.rapidpharmacovigilance.org/publication.php
71 Vaidya, S. S., J. J. Guo, P. C. Heaton, et al. 2010. Overview and Comparison of Post-Marketing Drug Safety Surveillance in Selected Developing and Well-Developed Countries. Drug Information Journal 44:519-533.
72 Olsson, S. 1999. National Pharmacovigilance Systems. 2nd ed. Uppsala: The Uppsala Monitoring Centre.
73 All of WHO full and associate members and Malawi (nonmember of the WHO program). A complete list is available at http://www.who-umc.org/DynPage.aspx?id=100653&mn1=7347&mn2=7252&mn3=7322&mn4=7442.

example, using the existing channel or resources for dissemination of medicine safety information. In Ghana, lack of collaboration between the PV center and the National Drug Information Resource Center led to inadequate use of the resources for PV activities as well as services such as reviewing the summary of product characteristics, labeling, and promotional materials for the initial registration of health products.[74]

A comprehensive national guideline or standard operating procedures (SOPs) for PV is necessary to standardize the provision of PV services and processes at all levels of the health system, but only 18 countries (39 percent) have national guidelines available. The lack of guidelines can affect the ability to coordinate stakeholders' contributions and implement PV activities in PHPs and health facilities.

A national medicine safety advisory committee provides technical advice and scientific opinion to the regulatory authorities and PV centers. A safety advisory committee exists in 18 countries (39 percent), but not all committees are fully functional. A functional committee is defined as one that meets regularly as scheduled, has an official document constituting the membership, and provides expert technical advice on medicine safety. A committee may exist but meets infrequently, often addresses issues in a sporadic manner, and does not have safety issues as the committee's key mandate. For example, the Expert Safety Review Panel in Kenya met twice in 2010 and only discussed issues related to clinical trials. In Tanzania, a PV committee was formed in October 2010 to exclusively address issues related to medicine safety, clinical pharmacology, and regulatory affairs that were previously handled by the Drug Registration Committee (table 3).

The development of sustainable structures and their optimal functioning are critical to PV systems.

PV is not well integrated into training curricula in medical, pharmacy, nursing, and public health schools in Africa. Only 7 of 15 academic institutions assessed in 8 countries had PV-related topics in the curriculum. Students are taught toxicity and ADRs of medicines as part of pharmacology, and some master's degree programs in pharmaceutical management and clinical pharmacy include lectures on history of PV and how to complete an ADR form. But most curricula do not cover key topics related to medicines safety such as PV in the regulatory system, risk identification, risk evaluation methods, and ensuring patient safety through risk management and communication.

PV is a cross-cutting issue that requires all stakeholders be encouraged to participate and share the responsibilities for its successful implementation as a part of a health system.[75] It involves regulatory authority, pharmaceutical industry, Ministry of Health, PHPs, academia, professional associations, donor organizations, WHO, patients, and representatives of civil society organizations and the general public. Coordination of all stakeholders is critical to ensure effective communication and leveraging resources among these interrelated bodies. However, such interactions among stakeholders seem limited and fragmented in many countries. Only 13 countries (28 percent) reported that there is a platform or strategy that enables coordination of PV activities at the national level. Often, vertical and individual project-driven activities were not known to the national PV center or linked with the overall national system. Various

74 Nwokike, J., and K. Eghan. 2010. Pharmacovigilance in Ghana: A Systems Analysis. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

75 The Global Fund. November 2010. Toward a Strategy on Pharmacovigilance. Presented during the WHO-Global Fund Stakeholders Meeting in Pharmacovigilance in Accra, Ghana.

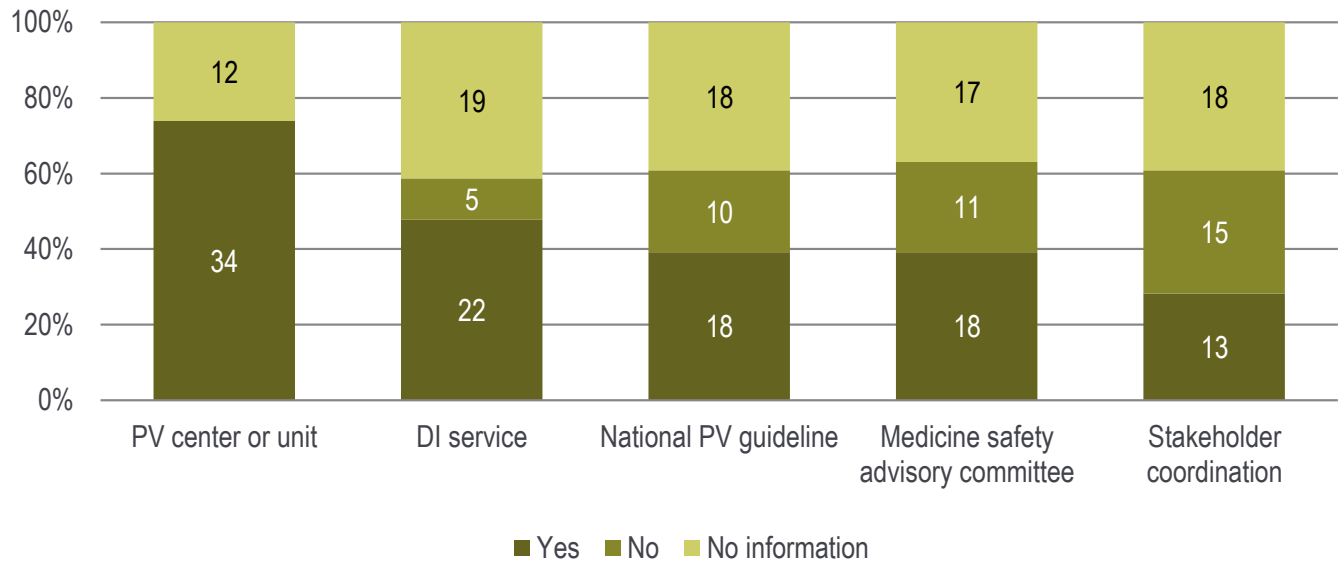
Table 3. Functions of Medicine Safety Advisory Committee

	Strengths	Weaknesses
Kenya	Clear mandate exists for the committee in regards to all medicine safety issues including PV and clinical trials	Limited activity for PV and more focus on clinical trials (no PV issues discussed during its meetings in 2010)
Uganda	Clear mandate of committee for PV and clinical trails Frequent meetings (5 times in the last half of 2010) Provide technical recommendations for safety issues presented by the secretariat (NDA) Promote PV to be included in curriculum	Role of committee should be strengthened to provide the NDA with a scientific opinion regarding causality assessment of ADR reports or recommend the necessary regulatory action or conducting further safety research
Ghana	Technical Advisory Committee (TAC) comprised of representatives from clinical pharmacy, research institutions, medical schools, teaching hospitals, public, industry, etc. Provide technical and regulatory recommendations for safety issues	Lack of members trained in PV on the committee TAC's inability to translate safety information from clinical trials to post-marketing safety monitoring
Burkina Faso	Not applicable	No committee established yet (in process)
Tanzania	Exclusively address issues related to medicine safety, clinical pharmacology, and regulatory affairs	Recently established in October 2010, but no formal activity yet
Nigeria	Clearly defined functions for the committee Broad membership from various fields (clinical medicines, pharmacy, pharmacology, toxicology, epidemiology, etc.) Members of the committee serving as coordinators in the various zones Functions including validation of causality assessment, recommending pharmacoepidemiology studies when necessary, recommending regulatory actions or information dissemination	Efforts should be made to sustain the activities of the committee (meeting held only twice in 2010, when scheduled quarterly)
Senegal	Two complementary committees—the national committee of PV to recommend regulatory decisions on safety issues to the Ministry of Health and the technical committee for PV to assess causality, evaluate risks, and transmit the outcome of assessment to the regulatory authority for further action Funding available for biannual meeting of the committee	Recently established and had its first meeting in December 2010 to discuss the role of the committee Need to strengthen its technical capacity to advise on safety issues and take regulatory decisions Need to establish effective communication between two committees
DRC	PV technical committee composed of experts from various fields Regularly review the technical reports from PV centers and provide expert opinion	National committee for drug safety composed of regulatory authority, PV center, Ministry of Health, poison center; others exist but not functional

initiatives, such as PEPFAR, the Global Fund, PMI, Bill & Melinda Gates Foundation (BMGF), and WHO, are making efforts to provide funding, resources, and technical support (see section Global Initiatives for Strengthning Pharmacovigilance Systems on page 79) for strengthening PV systems in African countries. Therefore, mapping all players to describe stakeholders' roles and responsibilities in-country can help identify existing efforts and gaps and maintain effective coordination to ensure those efforts are complementary and not duplicated.

Figure 10 shows the number of countries in SSA with basic elements of PV system, structure, and stakeholder coordination.

Figure 10. System, structure, and stakeholder coordination



Signal Generation and Data Management

Signal detection through reporting of suspected adverse events is the first step in the PV process, followed by signal evaluation and risk management. A signal is defined by WHO as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously,"[76] that may be a new adverse effect or a change in the character or frequency of an ADR that is already known. A signal can originate from many sources—spontaneous reports, literature, epidemiological study reports, patient records, registries, clinical trials, and cohort monitoring.[77]

All PV centers have ADR reporting forms. However, not all spontaneous reporting systems in countries address the full scope of PV, including product quality, medication errors, and treatment failures that can be reported by using the existing ADR form or a separate form. The result shows that reporting such events via existing PV systems is poor across the countries; only 50 percent report quality defects, 37 percent report medication errors, and 43 percent report treatment ineffectiveness (figure 11). Although countries claim that the current ADR forms are supposed to capture all medicine-related adverse events, actual forms that were reviewed do not often have sections dedicated to reporting those events or explicitly indicate that the form or indeed other forms should be used to report such events.

Coordination and collation of PV data was poor across the countries.

Developing a data management system that receives and collates PV data from all sources helps to utilize this information for signal detection and risk assessment.[66,77] In 23 countries (50 percent), the PV center or unit has a database, such as VigiFlow®[78]

76 The Uppsala Monitoring Centre, WHO. 2000. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Center. http://apps.who.int/medicinedocs/en/d/Jh2934e/

77 Cobert, B. L. and P. Biron. 2002. Pharmacovigilance from A to Z: Adverse Drug Event Surveillance. Blackwell Science.

78 VigiFlow is a web-based, individual case safety report management system developed and managed by the Uppsala Monitoring Center that is specially designed for use by national centers in the WHO Programme for International Drug Monitoring.

Figure 11. Scope of PV

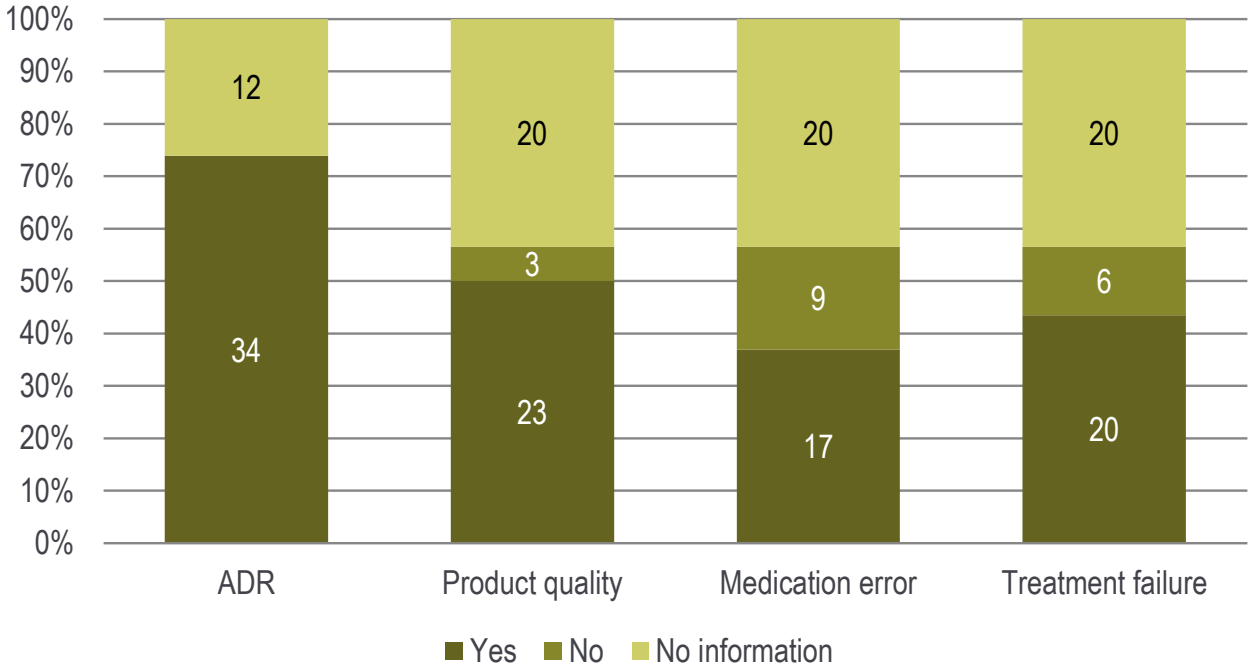
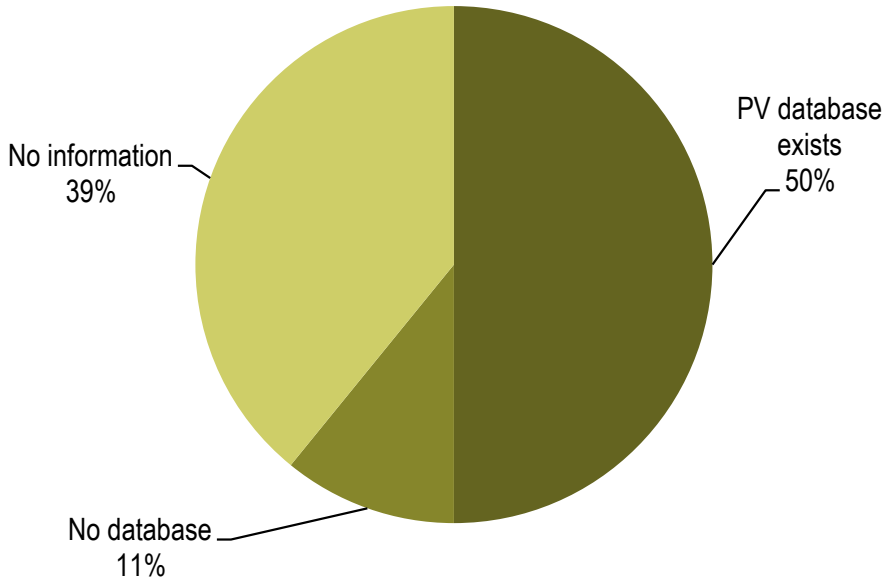


Figure 12. Existence of databases for PV in-country



to enter spontaneous ADR reports (figure 12). However, coordination and collation of PV data was poor across the countries. The central database in most countries did not contain data from various sources, such as reports from PHPs, clinical trials, AEFI from immunization programs, data from active surveillance, or PSURs from industry (tables 4 and 5). For example, a number of AEFIs followed by case investigation were not transmitted to the Uganda National Pharmacovigilance Center (NPC). PSURs submitted by pharmaceutical companies are not contained or stored in the central

Table 4. Coordination and Collation of PV Data from All Sources in the Country

Source of safety data	Number of countries with this information in central database
Spontaneous report	21
AEFI report	13
PSUR	8
Reports from PHPs	11
Active surveillance reports	5
Safety reports from clinical trials	6
Safety reports from global literature	4
Others	1

Table 5. Information Contained in PV Database in Selected Countries

Country	Sources of information in PV database
Burkina Faso	Spontaneous reports, AEFI reports, active surveillance reports, reports from pharmaceutical industry
	PSURs and data from clinical trials and PHPs are not found in the database
DRC	Spontaneous reports
	Need to improve data collation from all sources of safety information
Ghana	Spontaneous reports, AEFI reports, PSURs, reports from PHPs
	Clinical trials reports are kept in a separate tracking tool (spreadsheet) and there is no single database to collate them with other sources of information
Kenya	Spontaneous reports, AEFI reports, product quality reports, active surveillance, PSURs
	Data from PHPs and clinical trials are not found in the database
Nigeria	Spontaneous reports, AEFI reports, reports from PHPs
	Limited data from active surveillances, pharmaceutical industry, and clinical trials are found in the database
	No AEFI report received in 2010
Senegal	Spontaneous reports, AEFI reports, PSURs, active surveillance reports, reports from PHPs, reports from clinical trials
Tanzania	Spontaneous reports, AEFI reports
	Data from active surveillances, PHPs, clinical trials, and pharmaceutical industry (i.e., PSURs) are not found in the database
Uganda	Spontaneous reports, PSURs, reports from clinical trials
	Clinical trial reports are kept in a separate tracking tool (spreadsheet) and there is no single database to collate them with other sources of information
	AEFI reports, data from PHPs and active surveillances are not found in the database

databases in Nigeria, Tanzania, and Burkina Faso. SAE reports from clinical trials are sent to the national PV center in only six countries, so many countries are missing the opportunities to draw from the inherent advantages of linking pre-marketing and post-marketing safety data. Also, the use of standard terminologies and dictionaries for case definition is not common across all the countries. This is consistent with the findings of a recent study by the Brighton Collaboration, where 74% of respondents identified the need for harmonized methods and standardized case definitions in post-

marketing vaccine safety monitoring.[79] Therefore, efforts should be made to develop a system to coordinate disparate data from various sources as it will enhance the effective synthesis, interpretation, and use of safety information.

Risk Assessment and Evaluation

When a signal—particularly a potential signal that has significant public health importance—arises from one or multiple sources, it should be further investigated to evaluate the risk and benefit ratio. The procedure involves confirming the signal's validity, searching the appropriate literature and databases, gathering expert opinions, then making decisions, and taking appropriate actions to minimize the risks.[77] Lack of capacity for causality assessment, signal investigation, and other forms of data analysis and interpretation by national centers in Africa is widely recognized as a major challenge.[69,79]

A spontaneous report can generate a qualitative signal that provides new and important data, if the quality, completeness, and case causality are sufficient. In contrast, a quantitative signal can only be detected when an increase in frequency of its occurrence is observed from epidemiological studies, clinical trials, or cohort event monitoring (CEM).[80] The need for active surveillance becomes increasingly clear in identifying and quantifying important drug safety issues to complement spontaneous reporting.[81] Active surveillance includes a wide range of approaches to detect and evaluate risks, such as CEM, registries, sentinel sites, epidemiological studies (case control study, cohort study, cross sectional study), and phase 4 clinical trials.[53,82] The periodic review of the nature, severity, and specificity of adverse events through passive surveillance and evaluation of significant safety signals through active surveillance are fundamental to build a comprehensive and systematic PV and medicine safety system. Active approaches to surveillance are particularly valuable for PHPs, such as HIV/AIDS, TB, and malaria programs, and can provide useful information for evaluating new medicines for mass treatment and making evidence-based decisions involving revision of treatment guidelines. Recently, more PHPs are engaged in active surveillance with financial support from donors such as the Global Fund (see section PV in Public Health Programs, Page 61).

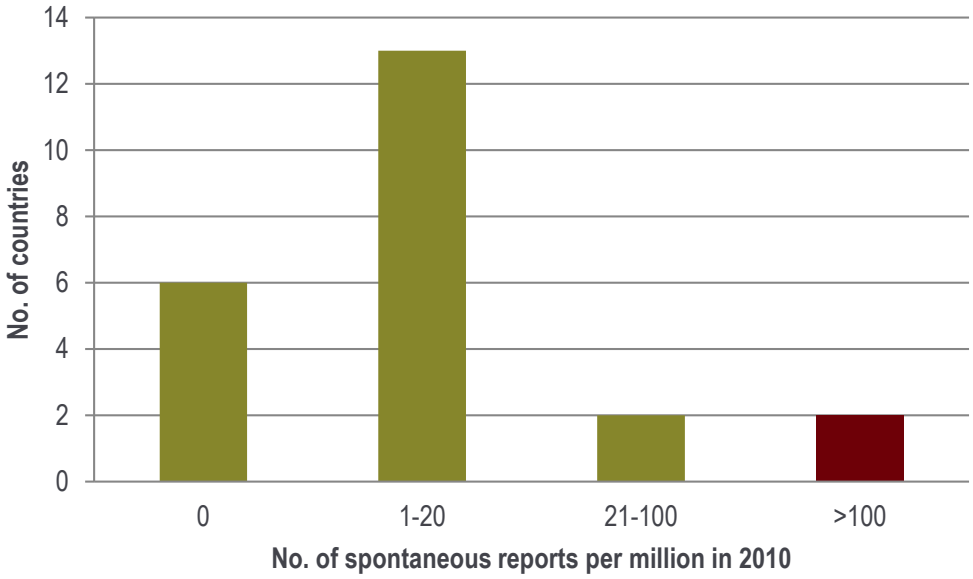
The need for active surveillance becomes increasingly clear in identifying and quantifying important drug safety issues to complement spontaneous reporting.

Low Reporting Rate in Spontaneous Reporting System

Although 23 countries in SSA are official members of the WHO Programme for International Drug Monitoring with the capacity to collect ADR reports, most of the countries still have weak ADR reporting practices. Using a threshold of 100 reports per million population per year,[83] only 2 countries (Namibia and Burkina Faso) generated the expected number of reports in 2010 (figure 13); 95 percent of reports in Burkina Faso were obtained from active surveillance during the new meningococcal

79 Jan Bonhoeffer, Yulin Li, Daniel Weibel. Brighton Collaboration. Capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries (personal communications with Dr. Li Yulin).
80 Meyboom, R. H., A. C. Eqberts, I. R. Edwards, et al. 1997. Principles of Signal Detection in Pharmacovigilance. Drug Safety 16(6):355-65.
81 The Uppsala Monitoring Centre, WHO. 2002. Importance of Pharmacovigilance: Safe Monitoring of Medicinal Products. Geneva: WHO.
82 European Medicines Agency. Pharmacovigilance Planning: Note for Guidance on Planning Pharmacovigilance Activities. 2006 CPMP/ICH/5716/03. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002818.pdf
83 However, the WHO Uppsala monitoring programme recommends that, ideally, the National Pharmacovigilance Centre should send over 200 reports per million inhabitants per year. http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558

Figure 13. Number of spontaneous reports received in 2010



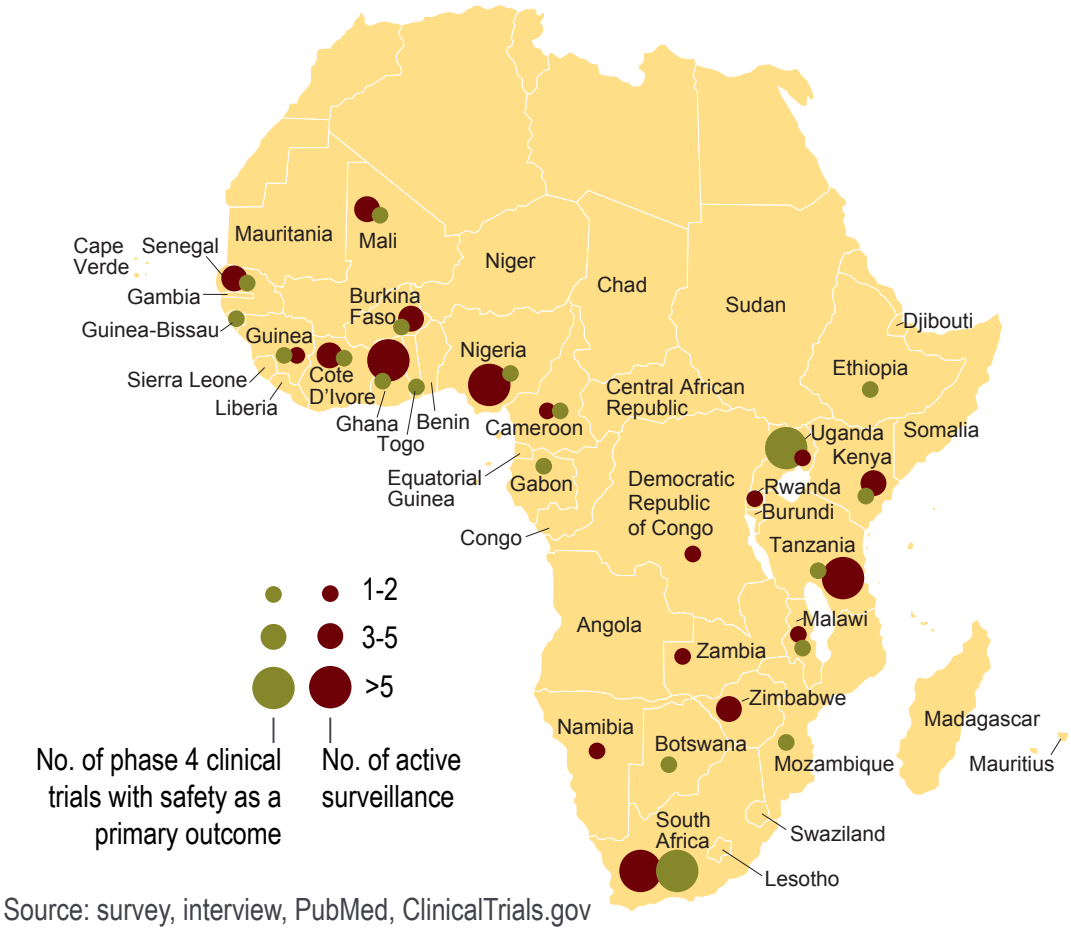
vaccination campaign, which means that the reporting rate might drop in the coming years without such initiatives. The reporting rate is significantly low in Africa, whereas 65 percent of other low- and middle-income countries receive more than 100 reports per million.[69] Acknowledging that PV is still relatively new to Africa and most PV centers became members of the WHO program after 2000, considerable effort and time are required to raise awareness among health care workers on the significance of reporting adverse events.

Ongoing Active Surveillance Activities and its Utilization

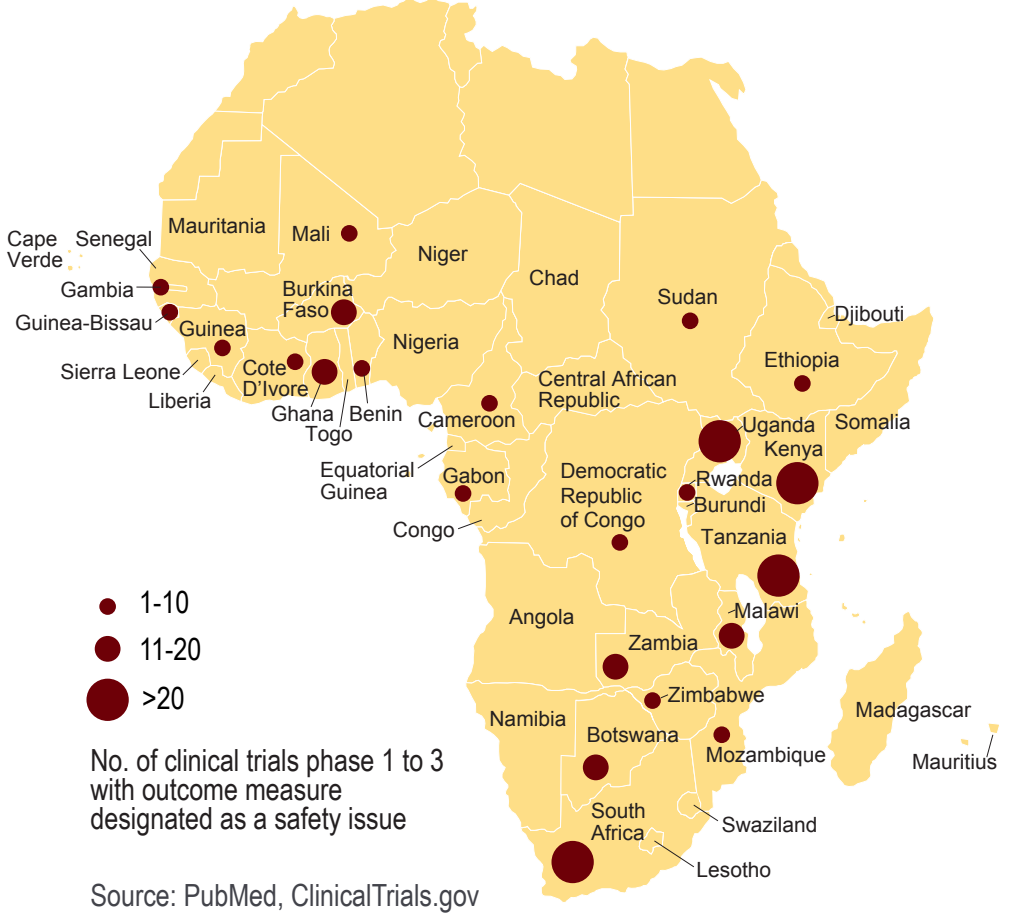
There is existing capacity in Africa to conduct medicine safety research (figure 14) that can help identify, evaluate, and confirm medicine-related risks. Active surveillance and phase 4 clinical trials to evaluate the safety and effectiveness of medicines have been conducted or are currently ongoing by academic institutions, PHPs, hospitals, and various international organizations in 22 countries (48 percent). When the studies were categorized according to the PHP areas they address, the majority (41 percent) were malaria related (figure 15). This study found that many of these activities were not known to national authorities, and data from these studies are not widely shared with PV centers. Subsequently, opportunities to use such new knowledge to inform regulatory actions or revise treatment guidelines are not being exploited. For better coordination of existing research capacity and resources, regional groups in Africa can be supported to develop networks that link research institutions and regulatory authorities, to build ongoing efforts to increase medicines research capacity,[48] and to harmonize medicines registration.

If reviewing results from spontaneous reporting and intensive monitoring does not bring about a conclusion that allows the signal to be confirmed, it may lead to a decision to undertake more structured studies to confirm, reject, or clarify the signal. SRAs routinely use findings from such studies to make evidence-based regulatory

Figure 14. Medicine safety research capacity in SSA

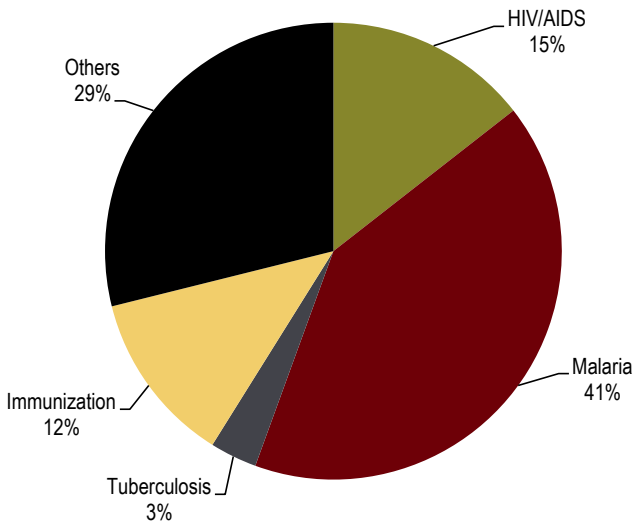


Source: survey, interview, PubMed, ClinicalTrials.gov



Source: PubMed, ClinicalTrials.gov

Figure 15. Active surveillances in relation to disease areas



The focus of formal epidemiological studies should be on high-priority safety concerns.

decisions.[84,85] This study's finding that active surveillance and phase 4 clinical trials have been conducted or are currently ongoing in 48 percent of countries presents a better picture compared to another recent study that found that only 15 percent of respondents reported conducting epidemiological studies on vaccine safety.[86] The difference could be attributed to the period and products covered and the types of studies included in the analysis. Because of the importance of these studies in informing regulatory decisions, the regulatory authorities can develop formal processes for evaluating significant safety issues in collaboration with stakeholders, in particular academic institutions and PHPs, to mobilize their existing resources. Given their high cost, length, and complexity, the focus of formal epidemiological studies should be on high-priority safety concerns to ensure that the limited resources are used efficiently and adequately.

Medicine use studies are applicable in evaluating safety signals. These studies describe how a medicine is distributed, prescribed, and used in a population, and how these factors influence clinical, social, and economic outcomes.[87] Utilization and consumption data can provide approximate denominators to estimate the frequency of adverse events attributable to a product and its safety in relation to a comparator.[77] Medicine use studies have been conducted in 13 (28 percent) of the 46 SSA countries during the last 5 years (figure 16). Countries need to make an effort to regularly collect, aggregate, and analyze this information to improve medicine safety and rational use.

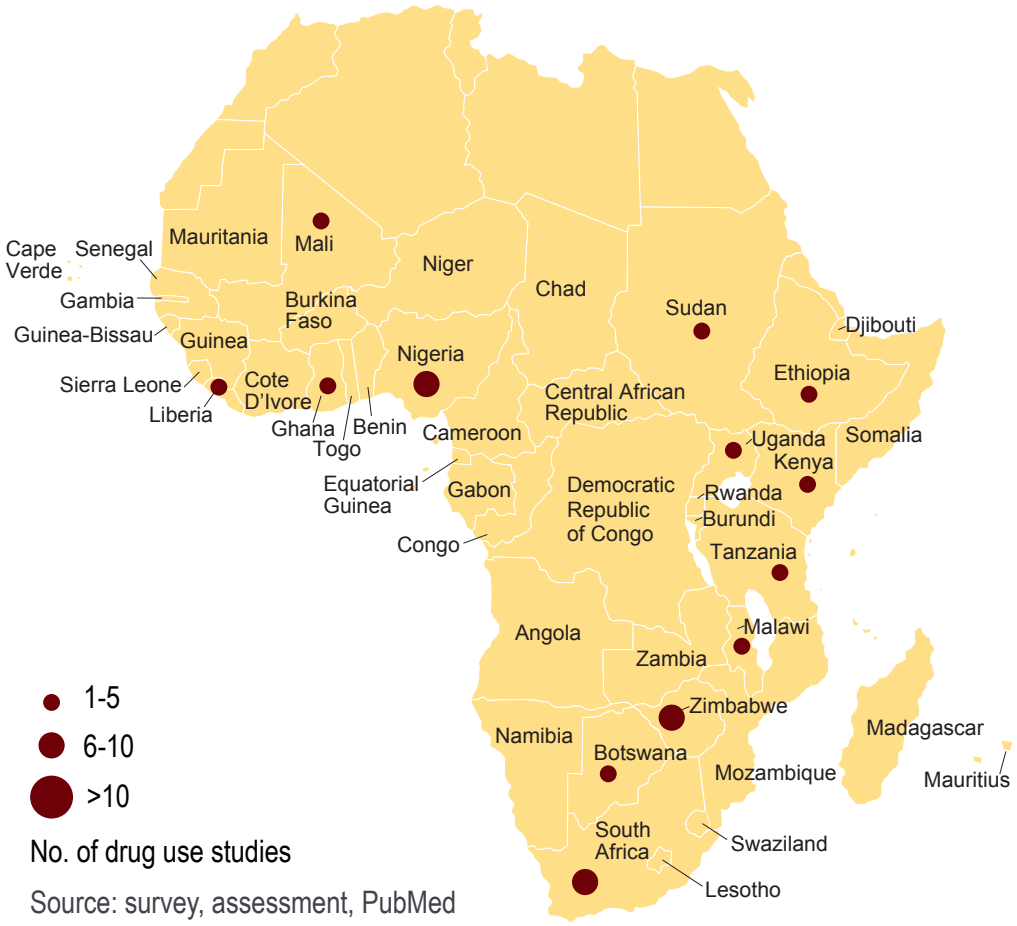
84 Clark, D. W, and M. Harrison-Woolrych. 2006. The Role of the New Zealand Intensive Medicines Monitoring Programme in Identification of Previously Unrecognised Signals of Adverse Drug Reactions. Current Drug Safety 1(2):169-78

85 US Food and Drug Administration (FDA). 2005. Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Available at http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf

86 The Brighton Collaboration draft report on the capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries reports that, when respondents were asked about the local minimal capacity to be achieved, 45% identified the need to improve the ability to link health care databases and 36% mentioned the ability to validate vaccine safety reports. There seemed to have been a great recognition of the need for epidemiological studies in the report as respondents expressed the need for the establishment of vaccine registries and secondary use of medical records in health databases as key priorities.

87 Strom, B. L. Pharmacoepidemiology, 3rd ed. 2000; p. 463–481; John Wiley and Sons, Ltd, New York, NY.

Figure 16. Drug use studies in SSA



Risk Management and Communication

Use of Information from Outside Sources

Medicine safety issues of local relevance identified from outside sources, such as another country or regional or international organizations, can be used to prevent any possible harm in the local population. Those sources of information that countries can easily access and use to inform locally relevant decisions are safety newsletters from WHO,[88] publications such as *Reaction Weekly*,[89] and safety alerts from SRAs,[90] such as the FDA[91] and EMA.[92] Countries without full capacity to generate signals and assess the risks can especially benefit from tracking, evaluating, and acting on

88 WHO. 2010. Pharmaceutical Newsletters, issues 1 to 6. Available at http://www.who.int/medicines/publications/newsletter/en/

89 This journal provides a comprehensive update of published ADRs case reports, drug withdrawals due to safety issues, labeling changes, safety research, and other current issues related to drug safety; the content is sourced from journals, media releases, regulatory agency and pharmaceutical company websites, and bulletins from national centers. Available at http://adisonline.com/reactions/pages/default.aspx

90 Members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Available at www.ich.org

91 FDA. 2010. Safety Alerts For Human Medical Products. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm196258.htm

92 EMA. Monthly reports of the CHMP Pharmacovigilance Working Party. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000198.jsp&mid=WC0b01ac0580033aa1

Table 6. Safety Alerts of Local Relevance from External Sources

Country	Examples of actions taken on safety issues based on outside sources
Burkina Faso	Suspension of marketing authorization for products for infants containing mucolytics (that may aggravate respiratory symptoms) and combination products of paracetamol, dextropropoxyphene, and benfluorex (source: AFSSAPS)
Ghana	Suspension of marketing authorization for rosiglitazone (source: EMA and FDA)
	Reclassification of metamizole sodium to prescription-only medicine (source: various literature)
	Safety alerts on didanosine, olanzapine, and cold and cough preparations for infants (source: FDA and WHO newsletters)
Kenya	Suspension of marketing authorization for rosiglitazone and sibutramine (source: EMA and FDA)
	Safety alerts on ceftriaxone, didanosine, saquinavir, simvastatin, and cough and cold preparations for infants (source: FDA and WHO newsletters)
Nigeria	Risk management activities recommended for rosiglitazone (source: EMA and FDA)
	Restriction on the use of cough syrup containing mucolytic for children under 2 years of age with subsequent change of labeling and recall of products with old label (source: AFSSAPS)
	Safety alerts on chloroxazone, immunoglobulin, phenytoin, ceftriaxone, ferrous sulfate, measles and rubella vaccines, hepatitis B vaccine, human papillomavirus vaccine, and sildenafil (source: *Reaction Weekly*)
Tanzania	License withdrawal for rosiglitazone and cough and cold preparations for infants (source: FDA and WHO newsletters)
Uganda	Suspension of marketing authorization for rosiglitazone (source: EMA and FDA)
	Safety alerts on interaction between proton pump inhibitors and clopidogrel, and an increased risk of muscle injury for patients taking the combination of amiodarone and simvastatin (source: WHO newsletter)
Senegal	Suspension of marketing authorization for rosiglitazone (source: EMA and FDA) and benfluorex because of increased risk of valvular heart disease (source: EMA)
	Label change for products containing mucolytics for children under 2 years and recall of old products (source: AFSSAPS)

Most countries studied do not have a systematic approach for processing safety alerts from external sources.

safety information from countries with more regulatory capacity. In the Brighton Collaboration study, 45 percent of respondents indicated that their countries are partially relying on vaccine safety information from other countries. The use of relevant regulatory intelligence and PV information from external source is an efficient strategy for timely regulatory action. Table 6 shows how countries have used the information from external sources to take regulatory actions, such as suspension of marketing authorization, reclassification, labeling change, license withdrawal, and communicating risks to public and health professionals.

The following two cases describe in more detail how some NRAs from developing countries have built on regulatory actions from SRAs. The Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSAPS; French Health Products Safety Agency) decided to contraindicate the use of mucolytic agents in children below 2 years of age because of the risk of aggravating respiratory symptoms. Following this decision to change the product label, several regulatory authorities in Africa took actions ranging from merely issuing a safety alert to withdrawal of license, taking as little as 1 day to act or as long as 10 months (table 7). Similarly, following EMA's decision to suspend marketing authorization of rosiglitazone and FDA's recommendation for risk management activities, several African countries decided either to withdraw the license or temporarily suspend the market authorization until more information was available for its risks and benefits ratio (table 8). The National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria made the regulatory decision on rosiglitazone within a month of FDA's, whereas it took almost 10 months in South

Table 7. Regulatory Actions Taken on Mucolytics

Country	Regulatory action taken					Communication	Time lag[a] (in days)
	No action	Label change	MA suspension	Withdrawal of product license	Risk management activities recommended		
Burkina Faso			■			Yes	175
Ghana	■					Yes	n/a
Nigeria		■			■	Yes	1
Tanzania				■		Yes	191
Senegal		■				Yes	308

[a]Time lag (number of days) between regulatory action taken by local regulatory authority and decision taken by the French medicine agency (AFSSAPS) to contraindicate the use of mucolytic agents in children below 2 years of age on April 28, 2010.

Table 8. Regulatory Action Taken on Rosiglitazone

Country	Regulatory action taken				Communication	Time lag[a] (in days)
	No action	MA suspension	Withdrawal of product license	Risk management activities recommended		
Ghana		■			■	67
Kenya		■			■	20
Namibia			■		■	48
Nigeria				■[b]	■	16
Senegal		■			■	19
South Africa			■		■	285
Tanzania			■		■	43
Uganda		■			■	114

[a]Time lag (number of days) between regulatory action taken by local regulatory authority and risk management activities recommended by US FDA on September 23, 2010.

[b]See box 1 for risk management activities recommended by NAFDAC.

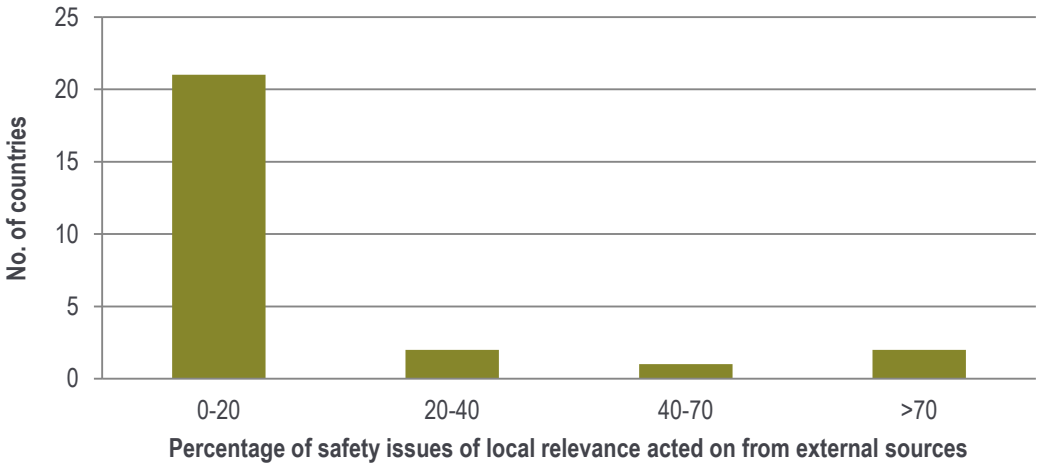
Africa. NRAs outside Africa, such as India, Indonesia, and Saudi Arabia, took regulatory actions either before or within two weeks of EMA's and FDA's actions. The average time lag for safety communication is longer for NRAs in SSA than other countries.[93]

Most countries studied do not have a systematic approach for processing safety alerts from external sources, particularly for those products registered and in use in their own country. Less than 20 percent of safety alerts from WHO pharmaceutical newsletters[94] were reviewed and acted on locally in most countries (figure 17). The countries might have decided not to take any action for some cases as the medicine is not widely

93 Nwokike, J. and A. Stergachis. 2011. Actions of the National Regulatory Authorities in Developing Countries Following US FDA and EMA Safety Alerts on Rosiglitazone, a poster presented at the 27th ICPE. Available at http://globalmedicines.org/2011/08/global-medicines-poster-at-the-27th-icpe-international-conference-on-pharmacoepidemiology-therapeutic-risk-management/

94 38 safety alerts included in 6 WHO pharmaceutical newsletters (2010) were used as a denominator. Available at http://www.who.int/medicines/publications/newsletter/en/

Figure 17. Percentage of safety alerts from external sources reviewed and acted on



Note: 38 safety alerts from 6 issues of WHO pharmaceutical newsletters in 2010 were used as a denominator

available or the risk is irrelevant in the local setting, yet there was no standardized process to review and make such decisions in most countries.

Alerts of local relevance should be handled by regularly scanning global safety literature, evaluating usage, risks, and benefits in the local market, and then, if necessary, acting by making regulatory decisions or communicating the risk to health workers. Figure 18 outlines the steps that may be considered in the processes for using safety alerts (for products with local public health importance) from external sources. Countries should create systems for timely management of new safety issues, particularly for products that are registered in domestic markets and that are being used by their citizens.

Risk Management

No consolidated or standardized procedure for risk management practices was in place.

An RMP is a set of activities designed to identify, characterize, prevent, or minimize risks related to the medicine; to assess the effectiveness of those interventions; and to communicate those risks to patients and health care providers. SRAs require such a plan as part of a medicine's approval process or for an approved product when new safety information emerges. For example, the FDA requires that a risk evaluation and mitigation strategy be developed to ensure that the benefits of a medicine outweigh its risks. RMPs may be required by EMA as part of the registration process.[95,96,97] Most RMPs may include additional activities designed to address an identified or potential serious risk associated with the medicine as well as routine monitoring activities such as—

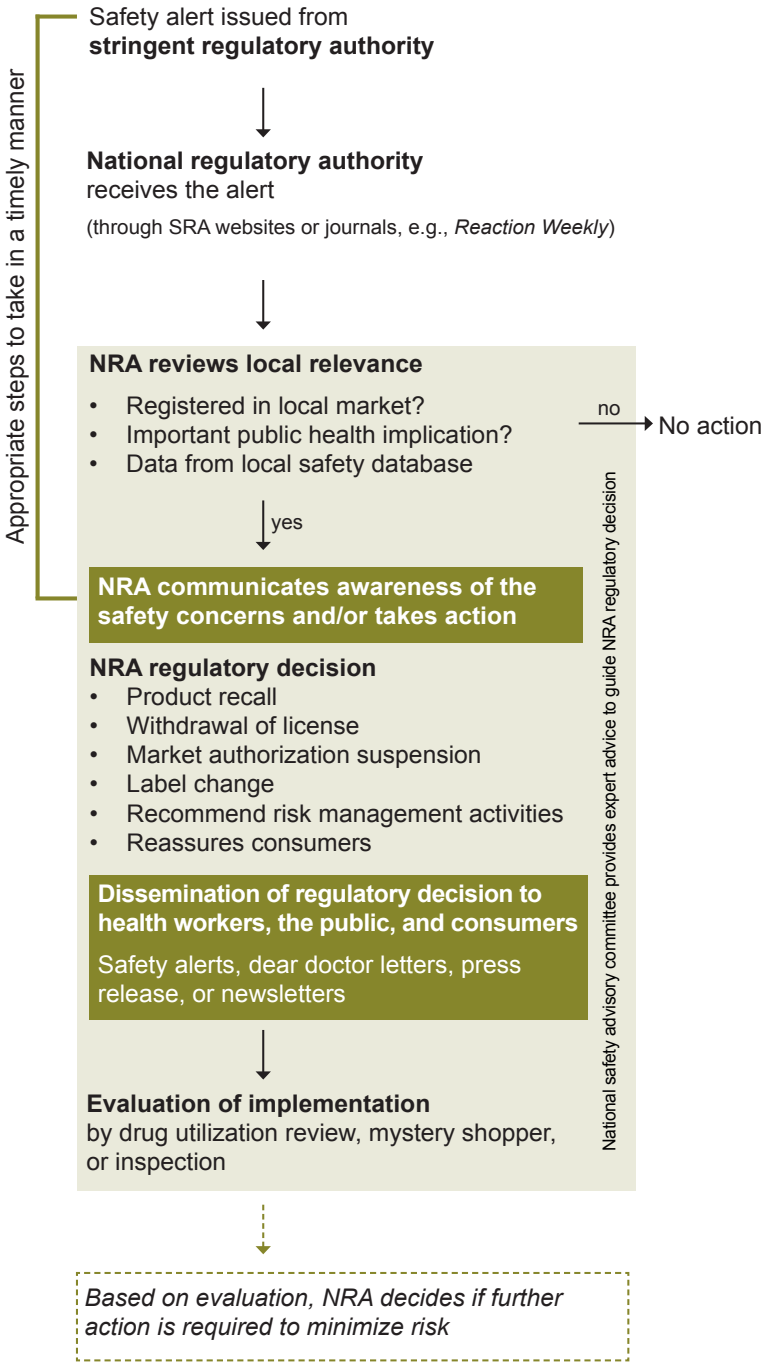
95 US FDA. Guidance for Industry: Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. Draft guidance. 2009. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

96 The International Conference on Harmonisation (ICH). ICH Harmonised Tripartite Guideline: Pharmacovigilance Planning—E2E (2004). Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf

97 EMA. The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use, Volume 9A, 2006. Available at http://ec.europa.eu/health/files/pharmacos/docs/doc2005/12-05/draft_of_volume_9a_12_2005_en.pdf

- Educational materials about medicine safety and its use (i.e., medication guide for patients, physician prescribing guide/checklists, or pharmacist dispensing guide/checklists)
- Communication guide for health care practitioners (i.e., dear doctor letters)
- Special training programs or certification for health care professionals
- Restricted use of the medicine in certain settings (i.e., dispensing the medicine only in a hospital or with evidence of safe use conditions)
- An implementation guide or system with a timetable

Figure 18. Processing new safety information from SRAs and making decisions on further action[93]



In eight countries where an in-depth assessment was conducted, we found that no consolidated or standardized procedure for risk management practices was in place, even though high-risk medicines are available. Some medicines are considered high risk because they are more likely to cause significant patient harm when used in error. Most countries do not have formal guidelines or procedures to mitigate, restrict, or supervise the use of high-risk medicines. Lack of the national risk management system resulted in poor documentation or implementation of practices in PHPs and health facilities handling high-risk medicines, although there are occasional good practices observed to some extent. For example, the safe injection practice guideline is available in immunization programs and hospitals. Prescribing and handling of medicines such as opiate analgesics, cytotoxic drugs, anticoagulants, and anesthetic agents are often restricted to specialists or certain levels of health facilities.

Even if high-risk medicines with a risk evaluation and mitigation strategy approved by the FDA are available in African markets, corresponding documented plans or procedures for these medicines were hardly found in these countries (table 9). A few regulatory authorities (i.e., Nigeria, Uganda, and Tanzania) requested MAHs to submit or implement

Table 9. High-Risk Medicines Registered in SSA Countries

Examples of medicines with approved risk evaluation and mitigation strategies by FDA	Registered in country? (*with some types of risk management activities)									
	Ethiopia	Ghana	Namibia	Tanzania	Uganda	Zambia	Kenya	Nigeria	Burkina Faso	Senegal
Rosiglitazone tab.	■	■		■	■	■	■	■*		■
Alendronate tab.			■		■	■	■			
Morphine sulfate oral solution				■*				n/a		n/a
Lopinavir and ritonavir tab. and oral solution	■	■	■	■	■	■	■	■*	■	■
Abacavir sulfate, lamivudine, zidovudine tab.			■*	■	■*	■	■	■*	■	■
Budesonide and formoterol inhaler		■	■	■	■	■	■	■		n/a
Carbamazepine tab. susp. ER tab.	■	■	■	■	■	■	■	■	■	■

Box 1. Example of Developing Risk Management Plan in Nigeria

Because medicines containing rosiglitazone increase cardiovascular events, both the EMA and FDA set up regulations concerning use of the medicine. This prompted NAFDAC to review the cases in the WHO global database and local ADR reports (*n* = 1) on bilateral leg swelling and peri-orbital swelling. Based on its review and discussion with the safety committee, NAFDAC decided to take the following steps to prevent harm and communicated its decision to the public and health care professionals. NAFDAC officials—

- Requested MAH to submit a report on its evaluation of patients exposed to the product by physicians
- Requested MAH to develop and submit a comprehensive risk mitigation plan
- Restricted the distribution of the products only to hospitals where a specialist can provide appropriate care to diabetic patients, including safety monitoring
- Advised health care professionals to switch to a safer alternative when there is no benefit for the patient and not to initiate the product to a new patient unless the benefits outweigh the risk

The extent to which the recommendations have been implemented in Nigeria has not yet been evaluated.

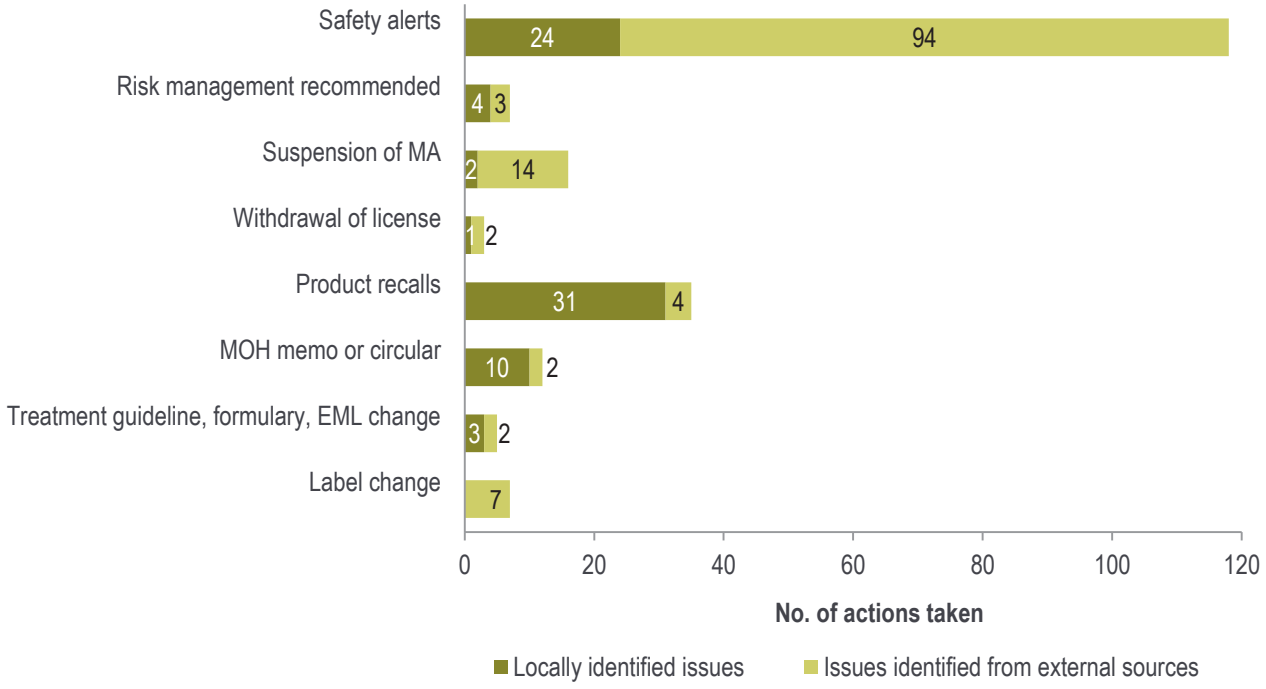
some type of RMP, but it occurred only sporadically and no such document submitted by MAHs was available for review in any of these countries. Box 1 illustrates the efforts in Nigeria to prevent the product's potential risks by implementing a set of action plans.

Outcomes of PV Activities

The effective use of PV data to improve safe use of medicines is increasingly emphasized. When implementing PV activities, adequate attention should be given to preventing or minimizing the risks of medicines. The immediate results of PV activities are preventative actions taken concerning medicine safety and quality, such as label change, changes or confirmation of safety of medicines in treatment guidelines, medicine formulary, essential medicines lists, product recalls, withdrawal of product licenses, and recommendations of risk management activities (figures 19 and 20). These preventive actions should eventually lead to improved patient safety and better health outcomes. Although a few countries are using the information, communicating to the public and health professionals, and taking actions based on the data from the PV activities, most countries still find it challenging. Nine countries (20 percent) publish medicine safety newsletters or bulletins, but only 6 countries actually published more than 50 percent of planned newsletters in 2010; 15 (33 percent) countries distributed safety alerts for public and health care workers to communicate the identified risks in 2010; and 17 countries (37 percent) took at least one form of regulatory action as a result of PV activities in 2010.

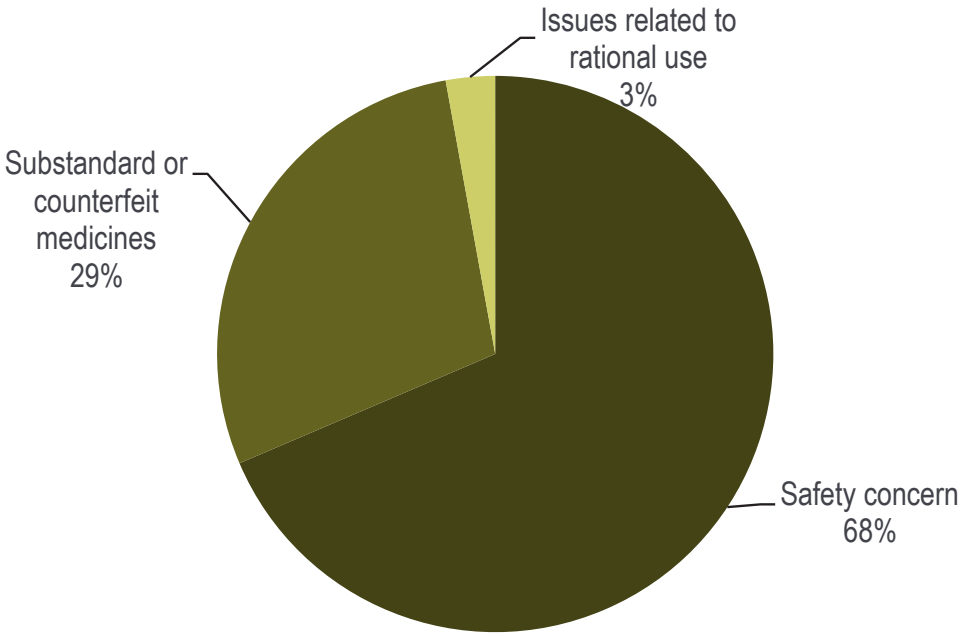
Several countries, such as Nigeria, Uganda, Kenya, and Namibia, have detected issues related to product quality, medication error, and toxicity of medicines by rigorous PV

Figure 19. Regulatory actions taken as a result of PV activities in 2010



Note: More than two actions could have been taken for the same issue.

Figure 20. Actions taken concerning safety or quality issue and rational use



Note: Regulatory actions taken as a result of PV activities in 2010 in figure 20 were classified according to main concerns related to safety, quality, and rational use.

activities from locally reported or generated information. For example, in Uganda, spontaneous reports and further investigation of the risks in patient records led to detection of medication errors related to quinine injection (box 2).

Similarly, Nigeria's PV system uncovered ADRs associated with medication errors and improper prescribing practices, resulting in a regulatory action to minimize the risk to the public (box 3).

The Kenya case (box 4) demonstrates how product quality issues can be identified through a PV system.

The experience in Namibia (box 5) shows the treatment guidelines update and development of risk management activities as a result of rigorous evaluation of PV data.

Box 2. Quinine Injection in Uganda

In 2009, the media reported an increase in cases of gluteal fibrosis, quadriceps fibrosis, and post-injection paralysis among children 1–14 years old in the Kumi region. The NPC investigated the cases in Kumi Hospital and identified 223 gluteal fibrosis cases, 11 quadriceps fibrosis cases, and 17 post-injection paralysis cases from 2008 to 2009. Several factors were considered as potential causes for the increased number of ADRs—injection by unqualified personnel, poor quality of the injection, irrational use of injection in the community, and unavailability of oral drugs (ACTs). NPC also searched for cases of surgical patients with a history of quinine use in the records of other regional hospitals. Recommendations were made to the Ministry of Health, including public education, restricting the use of quinine only to health centers that can monitor its use, and training health workers on proper administration of quinine. MOH recommended the change of administration site for quinine injection from the gluteus to the thigh; the change was also made in the national treatment guidelines (2010).

Box 3. Withdrawal of Gentamycin Injection in Nigeria

Gentamycin 280 mg/2 mL was extensively used for presumptive management of sexually transmitted infections and urinary tract infections as a daily dose for five consecutive days. Such a high dose of gentamycin was frequently prescribed because of convenience of administration over other lower strengths (10 mg, 40 mg, and 80 mg). The PV center received several reports of suspected ototoxicity and nephrotoxicity. The news media also raised concerns associated with the safety of gentamycin injection, reporting that a medical student lost the ability to hear after gentamycin 280 mg/2 mL had been injected for five days; the student was reportedly taken to the UK for treatment. After studying the situation and receiving recommendations from the drug safety advisory committee, NAFDAC decided to withdraw the license for all gentamycin 280 mg injections and also raise public awareness about appropriate use of the product. Other registered lower strengths of gentamycin injection were not affected. Safety alerts advised health professionals to discontinue the practice of prescribing and administering 280 mg gentamycin injection.

Box 4. Product Recall of Bupivacaine in Kenya

The Pharmacy and Poisons Board received reports from two hospitals regarding the lack of efficacy observed in the use of bupivacaine injection for spinal anesthesia. The board collected samples of the reported bupivacaine batch and sent it to the National Quality Control Laboratory for product quality testing. The samples failed the quality test, and the Pharmacy and Poisons Board decided to recall all batches of bupivacaine in Kenya in 2010.

Source: Interview, Kenya Pharmacovigilance Newsletter, Volume 1, Issue 2, February 2011, *The Kenya National Medicines Information and Pharmacovigilance Center Newsletter*, 1st ed., September 2011.

Box 5. Active Approach to Priority Medicine Safety Issue in Namibia

In 2007, the Ministry of Health and Social Services (MoHSS) of Namibia changed the first-line ARV regimen from stavudine to zidovudine (AZT). Spontaneous reports collected via routine passive surveillance indicated that anemia was the most frequently reported adverse event in patients receiving AZT and accounted for 51 percent of all ADR reports received by the Therapeutic Information and Pharmacovigilance Center between 2007 and 2009. MoHSS considered it an important safety signal and decided to further investigate the risk of anemia associated with AZT use. With technical assistance from USAID/SPS and the University of Washington, a retrospective probabilistic record linkage study was implemented by using existing electronic databases of regimens, hemoglobin values, and other risk factors.[a] The key findings were—

- The risk of severe anemia was high during the first three months of AZT use
- 46 percent of new cases of severe anemia that occurred among HAART users might be explained by AZT use in the first three months
- 6.7 percent of persons in the cohort developed anemia of any grade, whereas 1.2 percent developed severe anemia during the follow-up period[b]

MoHSS has recently decided to change the preferred first-line ARV treatment from AZT to a tenofovir-based regimen. However, MoHSS recognizes the important role of AZT as an alternative first-line treatment in Namibia and recommended implementing the following risk management activities based on the result of this study—

- ART clinics should ensure that patients receiving AZT have their hemoglobin monitored through counseling and schedule prescription refills to coincide with hemoglobin assessment dates
- ART clinics should improve hemoglobin assessment by using Hb meters at the sites
- Health care providers should closely monitor other risk factors for anemia in HIV patients
- ART clinics should periodically assess the quality of HIV care and adherence to ART guidelines[c]

The result of this study provided evidence-based information for reviewing treatment guidelines and designing risk management plans for patients receiving AZT containing treatment.[c]

[a] Source: The Namibia Medicines Watch, volume 2, issue 3, 2010. Available from http://www.nmrc.com.na/LinkClick.aspx?fileticket=ZwK6QULmYQs%3D&tabid=1350&language=en-US

[b] Source: Corbell, C., I. Katjitae, A. Mengistu, et al. 2011. Records linkage of electronic databases for the assessment of adverse effects of antiretroviral therapy in sub-Saharan Africa. *Pharmacoepidemiol Drug Saf.* 2011 Oct 19. doi: 10.1002/pds.2252 Available from http://onlinelibrary.wiley.com/doi/10.1002/pds.2252/abstract

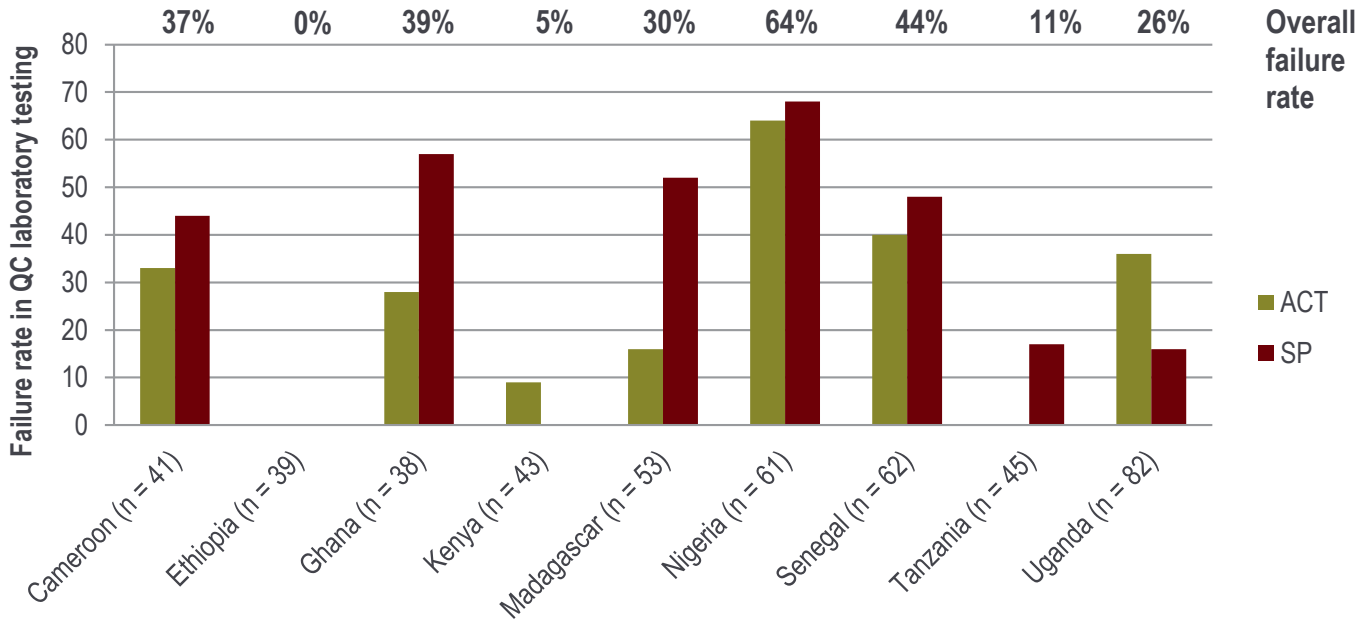
[c] MoHSS memorandum. 2011. Recommendations from Study on Risk of Anemia Associated with use of Zidovudine-based Antiretroviral Therapy in Namibia

Product Quality Monitoring Systems

Substandard and counterfeit medicine is becoming an increasing problem in SSA. Antimalarials have been particularly targeted by counterfeiters and 8 of the 12 common antimalarial drugs used worldwide were found to have been counterfeited.[98] Published estimates of the prevalence of counterfeit and poor-quality antimalarials in SSA were up to 64 percent.[99,100,101] According to the US Pharmacopeia's Drug Quality and Information (USP/DQI) program's survey of the quality of selected antimalarials, drug quality in private outlets and the informal sector may be more problematic in SSA where approximately 60 percent of all malaria episodes are initially treated by private providers.[102]

Figure 21 shows results of failure rates for ACTs and sulfadoxine-pyrimethamine from the WHO survey of the quality of selected antimalarial medicines circulating in six countries of SSA and the USP survey of antimalarials in three SSA countries, which used the same protocol.[99,101] The failure rates ranged from zero to 64 percent. The study showed a high failure rate of antimalarial medicines in the West African sub-

Figure 21. Results of QC laboratory testing in nine African countries



Source: WHO Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of SSA. WHO/EMP/QSM/2011.1, USP Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda.

98 Newton, P. N., M. Green, F. M, Fernandez, et al. 2006. Counterfeit Anti-Infective Drugs. Lancet Infectious Diseases 6 (9): 602–613.

99 WHO. Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa. 2011. Available at http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf

100 Bate, R., P. Coticeli, T. Richard. 2008. Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa. A Six Country Study. PloS ONE, 3:e2132.

101 United States Pharmacopeia Drug Quality and Information Program. 2010. Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda: November 2009. Rockville, Md.: The United States Pharmacopeial Convention. Available at http://www.usaid.gov/our_work/global_health/hs/publications/qamsa_report_1109.pdf

102 Onwujekwe, O., H. Kaur, N. Dike, et al. 2009. Quality of Anti-Malarial Drugs Provided by Public and Private Health Care Providers in South-East Nigeria. Malaria Journal 10;8:22.

region. Another interesting finding from the WHO survey was that WHO prequalified products showed significantly less failure rate (4 percent) compared to non-WHO prequalified products (60 percent). The WHO report on the study mentioned that the no-failure observed in Ethiopia may be attributed to strict implementation of regulations on products imported for use in its public hospitals and private pharmacies. The results of the study indicate that many countries in SSA are struggling with strengthening their regulatory systems to monitor the products in their market.

Figure 22 shows failure rate by source of products (domestic versus imported products). It shows that in general, domestically produced products exhibited higher failure rates than imported products. Regulatory systems need to be more transparent and uphold the same standards for local and imported products.

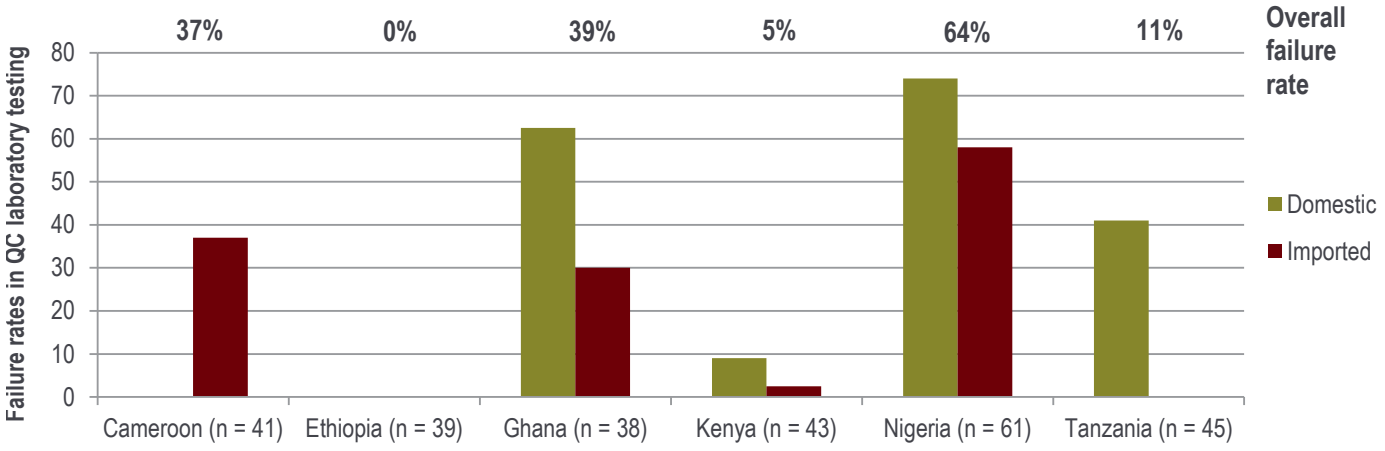
The quality concern also applies to ARVs. Counterfeit or substandard ARVs were found in Cote d'Ivoire, DRC, Ethiopia, Kenya, Uganda, and Zimbabwe.[103] Figure 23 shows that 3 to 14 percent of medicines randomly sampled by regulatory authorities in the selected countries failed product quality tests in 2010.

Quality assurance is an organized arrangement (processes and systems) of all elements that influence the quality of the product. It involves inspections for compliance with GMP, assessment of documentation on product quality submitted by the manufacturer, sampling and testing of medicines from the market or different entry points, and systematic evaluation of reported quality problems through the PV system.[104] According to the WHO assessment of 26 NMRAs in SSA, 54 percent have no quality monitoring system, only 27 percent test in case of complaints or as part of specific programs, and only 19 percent have systematic programs in place.

To facilitate global access to medicines of acceptable quality and safety, the WHO Prequalification of Medicines Programme, launched in 2001, evaluates products

Many countries in SSA are struggling with strengthening their regulatory systems to monitor the products in their market

Figure 22. Failure rate of domestically produced and imported product samples

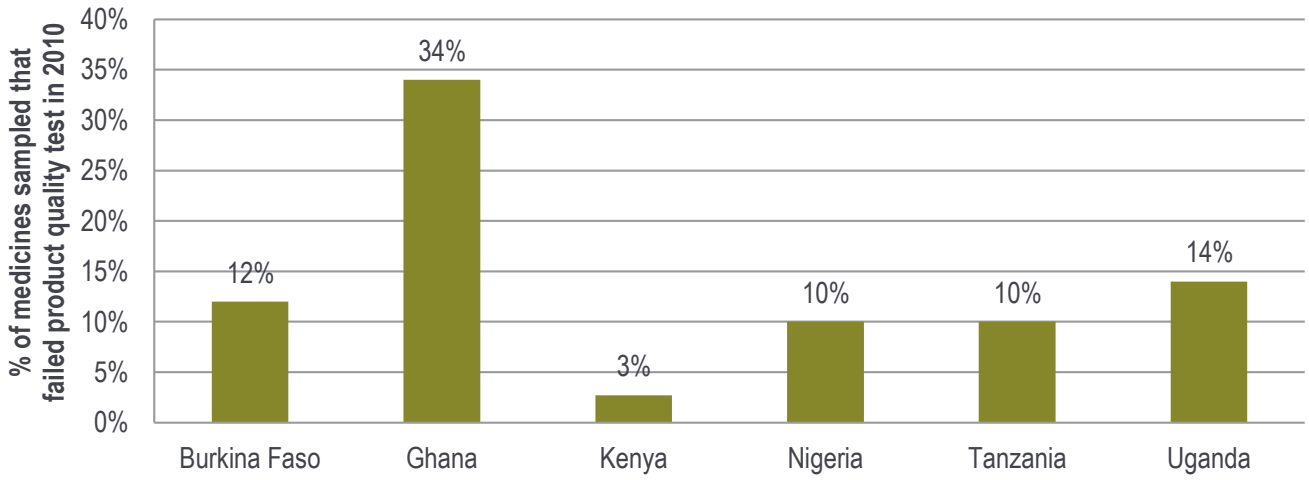


Source: WHO Survey of the quality of selected antimalarial medicines circulating in six countries of SSA. WHO/EMP/QSM/2011.1

103 WHO. 2007. Survey of the Quality of Antiretroviral Medicines Circulating in Selected African Countries. http://www.who.int/medicines/publications/ARV_survey.pdf

104 Alghabban, A. 2004. Dictionary of Pharmacovigilance, 1st ed. New York, NY: Pharmaceutical Press, p. 400-401.

Figure 23. Product quality test results in 2010



Source: Data provided from staff members of NMRAs.

according to WHO-recommended standards and compliance with GMP and good clinical practices. It provides the list of prequalified medicines used for HIV/AIDS, TB, malaria, and reproductive health that are, in principle, acceptable for procurement by United Nations agencies or any other organizations involved in bulk purchasing of medicines at country and international level.[105] For example, the Global Fund quality assurance policy requires that pharmaceutical products purchased with the Global Fund resources should be on the WHO prequalification list or approved by SRA.[106]

Although the WHO Prequalification of Medicines Programme is an important tool for procurement of quality medicines, the process does not guarantee the quality of products procured from the listed suppliers. This is particularly true when there is no adequate supply chain management in place, including appropriate storage conditions and efficient delivery systems. Therefore, ongoing and comprehensive product quality assurance at all stages of the product cycle is critical. Figure 24 describes an approach for pharmaceutical product quality surveillance throughout the product lifecycle. A systematic and comprehensive quality surveillance system can be achieved through passive and active approaches. For the passive approach, the spontaneous reporting systems can be beneficial in empowering health workers and consumers to report products of suspected quality. Using the spontaneous reporting system to monitor product quality has yielded useful results in Kenya.[107]

A product quality survey[108] is an example of an active approach that regulatory authorities can use to monitor medicines quality. Quality surveys of marketed products can provide information on proper handling of medicines during

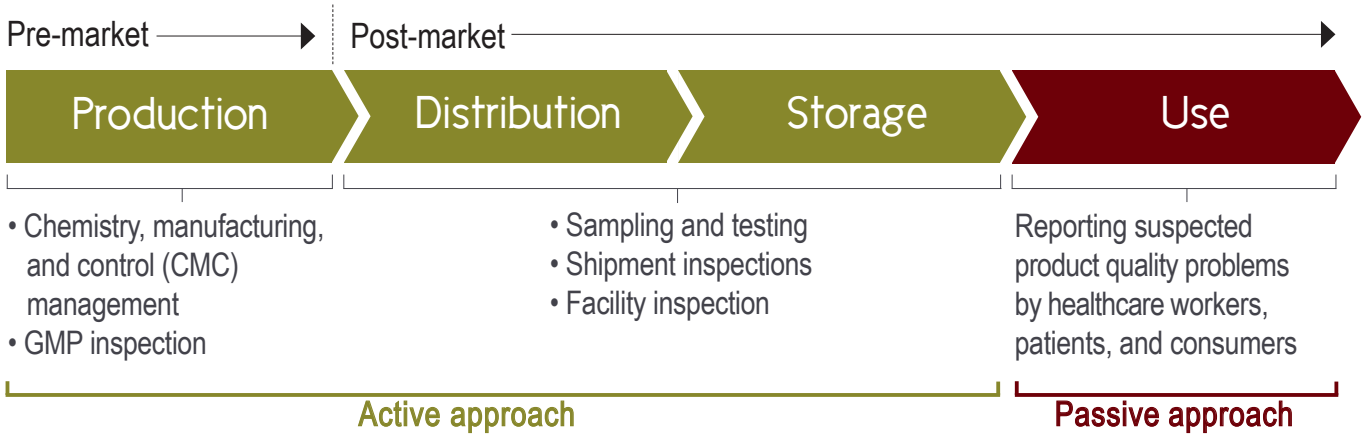
105 WHO. Prequalification of Medicines Program (PQP) Facts and Figures for 2010. Available at http://apps.who.int/prequal/info_general/documents/2010_PQP-Summary.pdf

106 The Global Fund. 2010. Quality Assurance Policy for Pharmaceutical Products. Available at http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/#QA_Policy

107 Kenya Pharmacy and Poison Board. Pharmacovigilance Newsletters. Vol 1. Issue 2 & Special ed. Available from http://www.pharmacyboardkenya.org/index.php?id=126

108 A study that has sampled and tested the quality of medicines according to a standard procedure of quality surveillance.

Figure 24. Pharmaceutical product quality surveillance



distribution and storage. Of SSA countries, 37 percent (17 countries) reported that product quality surveys were carried out in the last 5 years.

There are various initiatives to strengthen the gaps in quality assurance and quality control systems in SSA. For example, the United States Pharmacopeia (USP)'s Promoting the Quality of Medicines (PQM) program has supported Benin, Ethiopia, Ghana, Kenya, Liberia, Mali, Mozambique, Rwanda, and Tanzania in increasing the ability of their quality control laboratories to analyze medicines, establish product quality monitoring systems, and use simple and rapid screening methods such as Minilab®. The PQM program has developed the Medicines Quality Monitoring database for tracking information on the quality of medicines in the market.[109] There are also other emerging initiatives like the use of handheld near-infrared and Raman spectroscopies. These methods are currently being implemented in several African countries including Nigeria.[110] Also, in Ghana, Kenya, and Nigeria, consumers can verify whether the product is genuine or counterfeit by text messaging the authentication code on the product package to the toll-free number leased from telecom operators and directed to the mPedigree application. Then, mPedigree connects the mobile networks to a central registry that stores information on the branded medicines of participating drug manufacturers.[111,112]

PV in Public Health Programs

Data collected from national malaria, HIV/AIDS, TB, and immunization programs in eight SSA countries show to what extent PHPs are involved in PV. Of 32 PHPs studied, only 12 programs (38 percent) have policy statements related to PV. Fewer national policy documents for HIV/AIDS and TB include statements for monitoring ADRs or PV-related activities than those for malaria and immunization programs

109 USP. Promoting the Quality of Medicines. Medicines Quality Monitoring Database. Available from http://www.usp.org/worldwide/medQualityDatabase/

110 Taylor P. NAFDAC praises TruScan role in Nigerian counterfeit fight. SecuringPharma. Published on Apr 15, 2010. Available at http://www.securingpharma.com/nafdac-praises-truscan-role-in-nigerian-counterfeit-fight/s40/a443/

111 mPedigree website. Available at http://www.mpedigree.net/mpedigree/index.php?option=com_content&view=article&id=46&Itemid=53

112 Orhii, P. 2010. Progress and Policy at NAFDAC, presented at 5th Global Forum on Anti-Counterfeiting.

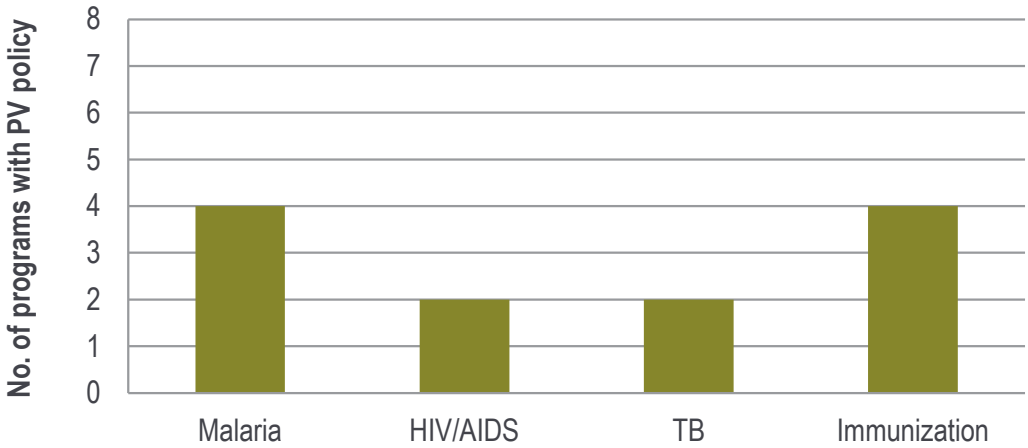
(figure 25). The PV unit or a focal person designated for PV (usually a program pharmacist, pharmaceutical unit, or case management unit) exists in less than half of HIV/AIDS, TB, and malaria programs whereas the designated unit or person exists in six of eight immunization programs (figure 26). In most immunization programs, ensuring vaccine safety was a routine activity of surveillance units. In Uganda, an expert committee reviewed AEFI cases and made appropriate recommendations. A budget designated for PV or as a part of other disease surveillance activities was available in malaria and immunization programs, often supported by the Global Fund, PMI, CDC, Global Alliance for Vaccines and Immunization (GAVI), and the Ministry of Health. A national adverse event reporting form was used in most programs and an AEFI form or case reporting form was used in immunization programs.

Although limited efforts exist in PHPs for evaluating medicine safety, quality, and rational use, it is apparent that a number of them are now engaged in active surveillance activities, such as establishing sentinel sites, CEM, and registries, particularly with malaria and immunization programs. Six malaria programs and six immunization programs in eight countries have conducted active surveillance in the last five years. Financial support from donors such as the Global Fund and GAVI as well as technical support from WHO and other international organizations might have contributed to this integration of PV in PHPs.[113]

Six malaria programs and six immunization programs in eight countries have conducted active surveillance in the last five years.

However, HIV/AIDS programs' engagement in PV is still insufficient and much less than malaria or immunization programs; only two HIV/AIDS programs have conducted active surveillance in the last five years (figure 27). This corresponds to the finding from the analysis of the Global Fund Round 9 proposals that 60 percent of malaria proposals have included more than one PV activity, whereas only 37 percent and 45 percent of HIV/AIDS and TB proposals, respectively, mentioned those.[114]

Figure 25. PHPs with policy framework for PV



Source: National malaria, HIV/AIDS, tuberculosis, and immunization policy documents, strategic plans, and treatment guidelines in Burkina Faso, DRC, Ghana, Kenya, Nigeria, Senegal, Tanzania, and Uganda.

113 Bakare, N., I. R. Edwards, A. Stergachis, et al. 2011. Global Pharmacovigilance for Antiretroviral Drugs: Overcoming Contrasting Priorities. PLoS Med 8(7): e1001054. doi:10.1371/journal.pmed.1001054

114 The Global Fund. An analysis of grant applications in the Global Fund database (R4 to R9) of the extent of their inclusion of pharmacovigilance activities. November 2010. Executive summary presented during WHO-Global Fund Stakeholders Meeting in Pharmacovigilance in Accra, Ghana.

Little is known about the toxicity, intolerance, and drug-drug interaction of newly employed ARVs in SSA. Without establishing robust mechanisms to monitor and assess the risks and benefits of new ARVs in the disease programs in collaboration with national PV centers, the occurrence of SAEs in the context of a rapid scale-up of ARVs can significantly damage the credibility of the program.[115] In South Africa, the ARV therapy program has adopted PV indicators for monitoring medicines safety.[116]

Figure 26. PV structure, guideline, and reporting form in PHPs

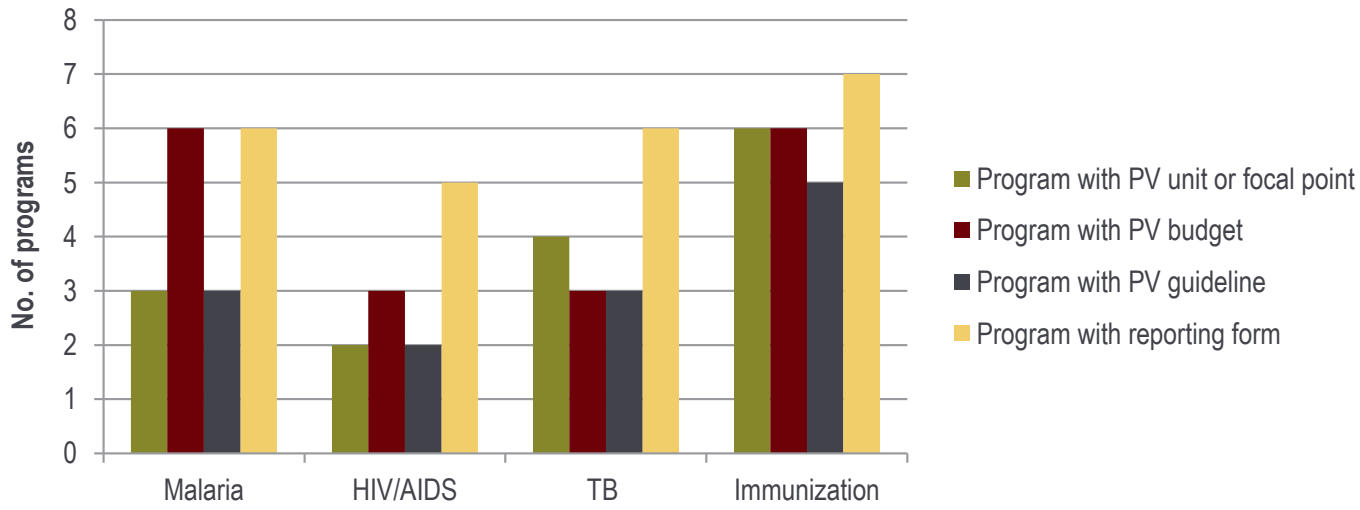
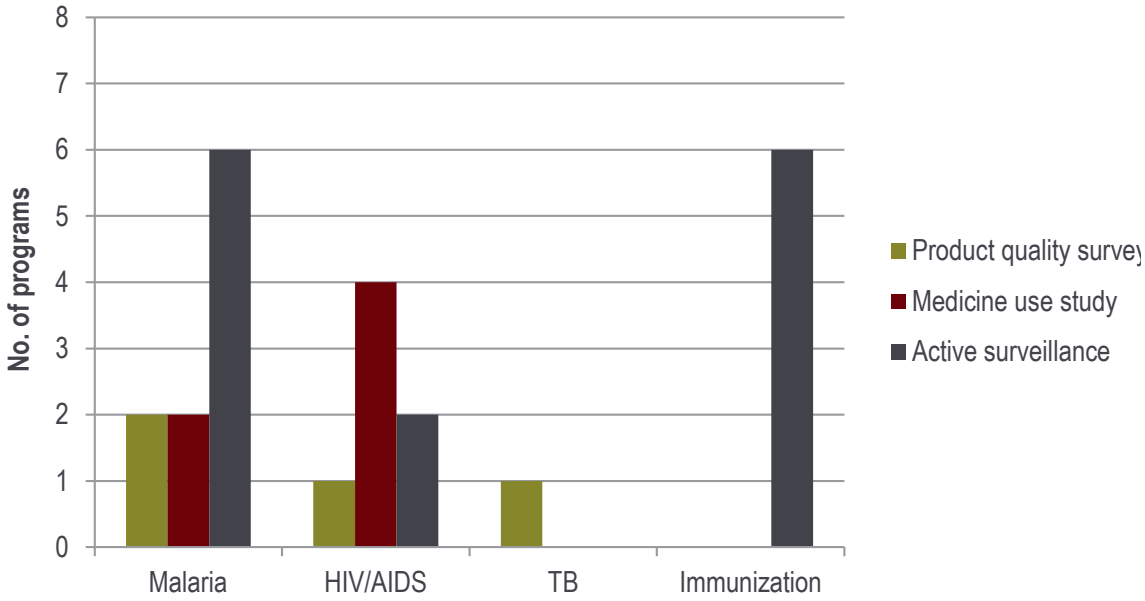


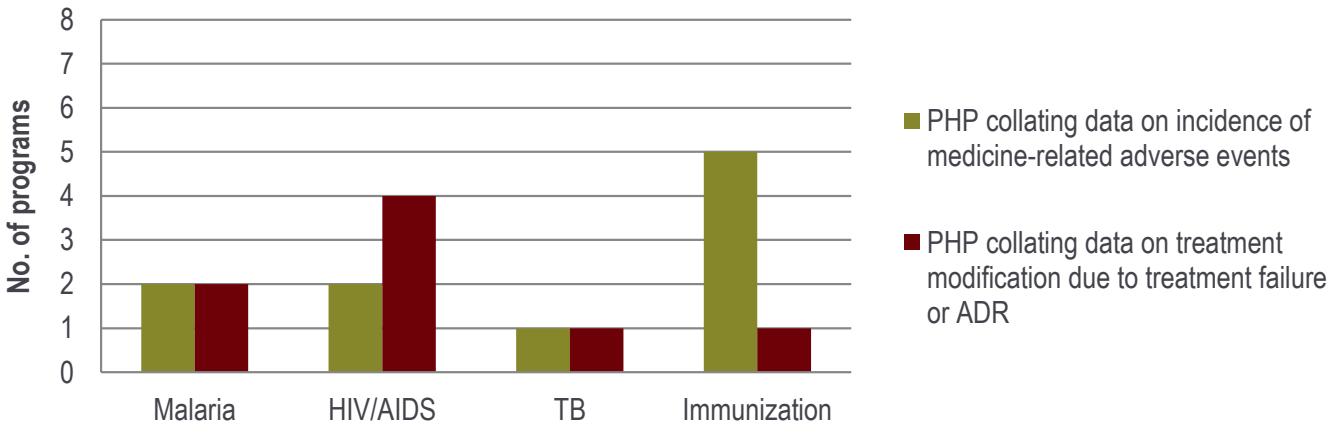
Figure 27. Risk evaluation activities conducted in PHPs in the last five years



115 WHO. 2009. A Practical Handbook on the Pharmacovigilance of Antiretroviral Medicines. http://whqlibdoc.who.int/publications/2009/9789241547949_eng.pdf

116 Department of Health. Monitoring and Evaluation Framework for the Comprehensive HIV and AIDS Care, Management, and Treatment Program for South Africa. 2004. Available at http://www.hst.org.za/uploads/files/monitorevaluation.pdf

Figure 28. Documenting PV data in PHPs



Note: Treatment modification not applicable to immunization program

Reporting based on treatment modification/ interruption can be one feasible approach to monitor ADRs in a large observational HIV cohort

PHPs should collate and document the proportion of patients who experienced drug-related adverse events among the total number of patients receiving the treatment.[117] This information can then be used to calculate rates of incidence of ADRs with a known denominator (number of patients treated) to identify or evaluate medicine safety issues. Very few programs (only 5 of all malaria, HIV/AIDS, and TB programs) provided such data. It may be recorded in individual patient files, but unavailability of such data means that there is no effort or strategy to routinely collate and aggregate adverse event data in PHPs. In contrast, 5 of 8 immunization programs monitor, collect, and document AEFI data (from 2 to 7 per million population) as part of routine monitoring and evaluation activities (figure 28).

Data on treatment modification/interruption was relatively well documented in HIV/AIDS programs (0.9 percent to 4.33 percent of patients experienced at least one treatment modification/ interruption) than other disease programs. The reporting of ADRs based on treatment modification/interruption can be one feasible approach to monitor ADRs in a large observational HIV cohort, as drug-related toxicity is the most common cause of treatment modification/interruption in patients undergoing ART in SSA.[12,118,119]

PHPs and national PV centers do not share information. ADR reports from most PHPs were not sent to the national PV center. For example, immunization programs share safety data with WHO by sending the AEFI to the global database, but not to the national PV center. Only two of five immunization programs that collected AEFI reports in 2010 transmitted the data to national PV centers.

Risk management activities, including using information to review treatment guidelines, developing risk mitigation plans for high-risk medicines, and training and communication of safety information to health care workers, are almost nonexistent

117 WHO. Safety of Medicines in Public Health Programs: Pharmacovigilance, an Essential Tool. 2006. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf

118 Messou, E., X. Anglaret, J. Duvignac, et al. 2010. Antiretroviral Treatment Changes in Adults from Cote d'Ivoire: The Roles of Tuberculosis and Pregnancy. AIDS 2010 Jan 2; 24(1): 93–99.

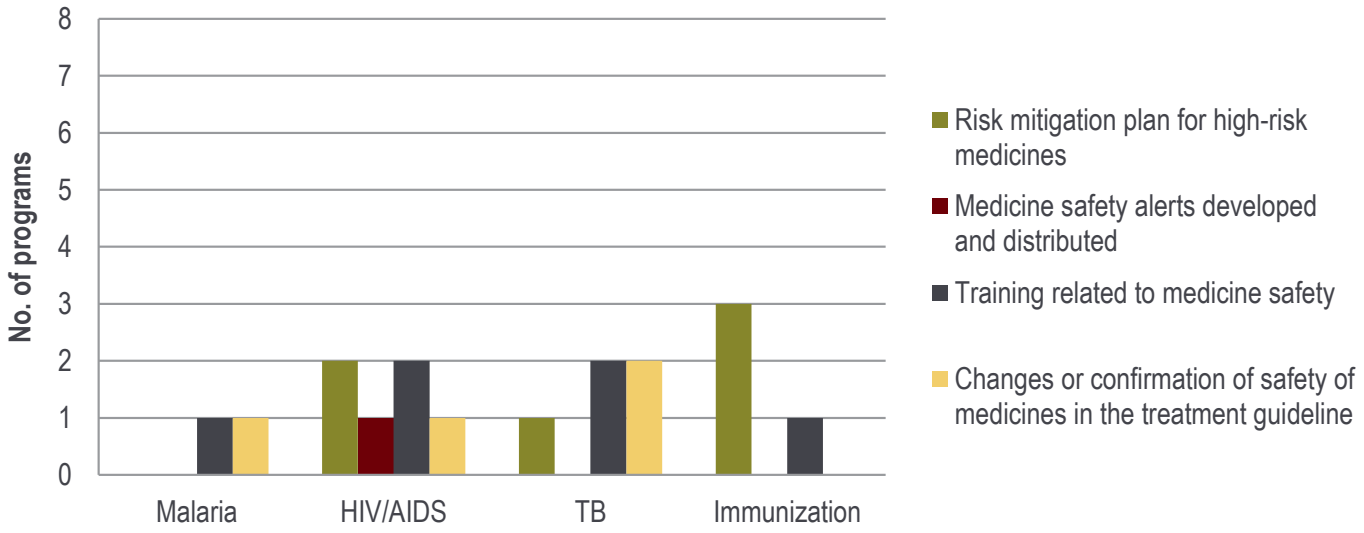
119 Braitstein, P. P. Ayuo, A. Mwangi, et al. 2010. Sustainability of First-Line Antiretroviral Regimens: Findings from a Large HIV Treatment Program in Western Kenya. Journal of Acquired Immune Deficiency Syndrome 53(2): 254–259.

in disease programs (figure 29). Only one program surveyed communicated safety issues to health care workers in 2010, including alerts received from the national PV center. Medicine safety actions taken in PHPs include removal of stavudine from first-line regimens in Kenya (box 6), reduction of amodiaquine dose in ACT because of the higher incidence of ADRs associated with high doses in Nigeria, switching from ethambutol to rifampicin in primary TB treatment in Kenya, and switching from ofloxacin to levofloxacin for MDR-TB treatment in Kenya.

Monitoring Vaccine Safety

As immunization programs have become more successful and provided highly cost-effective interventions, concern has been increasing over the capacity of developing countries to ensure safe use of vaccines, in particular, those newly prequalified,

Figure 29. Risk management and communication in PHPs



Box 6. ART Guideline Change in Kenya

In Kenya, 350,000 patients are currently on ART with more than 95 percent of patients starting a stavudine-based first-line regimen. With the greatest drop in consumption of stavudine since the issue of global reports on its toxicity in November 2009, the national HIV/AIDS program (NASCOP) decided to review local experiences as well as the global data on the toxicity of stavudine. Data from various programs implemented in Kenya found the following—

- 15–25 percent of patients had a regimen change since 2003; treatment change occurred in patients on stavudine-based regimen more often than zidovudine-based regimen or others; 6.3–25 percent of patients on stavudine experienced treatment change and 4.4–13 percent of patients on zidovudine switched to another regimen
- 52–67 percent of patients on stavudine developed toxicities to it over 5 years; treatment change was mainly due to ADRs of stavudine; ADRs accounted for 67–89 percent of documented reasons for treatment change; the most common ADRs were peripheral neuropathy, rash, lipodystrophy, hyperlactatemia, hepatotoxicity, nausea, and dizziness

Based on these findings, NASCOP decided to put new patients on zidovudine- or tenofovir-based regimens and gradually phase out stavudine over the next 3–5 years with intensive monitoring of toxicities.

Source: Presentation to NASCOP for ART guideline revision, April 2010

introduced, or expanded.[120] Also, a growing number of vaccines manufactured and supplied by companies in developing countries are now widely available in any part of the world. For example, a company in Senegal manufactures yellow fever vaccines prequalified by WHO and supplies the products to other African countries.[121]

As stated above, immunization programs in SSA have incorporated the safety monitoring of vaccines in routine surveillance activities—six of eight immunization programs surveyed had a PV unit or focal point with a dedicated budget for safety surveillance, five programs had systems to monitor and collate AEFI data as part of routine monitoring and evaluation activities, and three programs have carried out active surveillances. For example, active surveillance was implemented to ensure newly introduced meningitis vaccine in Burkina Faso (box 7).

The common challenge to monitoring vaccine safety includes the lack of information sharing and collaboration between the regulatory authority, the vaccine program, and the national PV center. Another major challenge is safety communication and how to manage safety concerns from the public about vaccines. Box 8 presents an example of importance of appropriate and proactive communication on vaccine safety in Nigeria. Countries should be supported to strengthen the collaboration among relevant stakeholders, provide more evidence-based information, and improve communication strategies to address suspicions about vaccine safety.

Six of eight immunization programs surveyed had a PV unit or focal point with a dedicated budget for safety surveillance

There are several ongoing global initiatives to strengthen vaccine safety monitoring in developing countries. WHO established a Global Network for Post-Surveillance of Newly Prequalified Vaccines in 2009 with support from the BMGF. This initiative has been implemented in 11 selected low- and middle-income countries, including Uganda and Senegal, to establish standardized post-marketing surveillance of vaccine safety. The countries can share information about AEFI by submitting the data to the Uppsala Monitoring Centre database. The network also supports the collaboration among national immunization programs, regulatory authorities, and national PV centers. On a wider scale, the initiative aims to share the data with other countries, vaccine manufacturers, and United Nations vaccine supply agencies.[122] More recently, WHO, together with other stakeholders, introduced the Global Vaccine Safety Blueprint Project to analyze

Box 7. Active Surveillance of a New Meningitis Vaccine in Burkina Faso

The Meningitis Vaccine Project, a partnership between WHO and the Program for Appropriate Technology in Health (PATH), introduced a new meningococcal A conjugate vaccine, MenAfriVac™ in Burkina Faso, Mali, and Nigeria in 2010. Recognizing the importance of safety monitoring of new vaccines, the DGPML implemented the active surveillance of AEFI in close collaboration with WHO and the immunization program (Service de la prevention par la vaccination) during mass immunization campaigns. The PV unit was involved in developing a protocol and tools for monitoring AEFI, training the members of the National Vaccine Committee and health care workers, and collecting and analyzing AEFIs. During the vaccination campaigns, the PV unit had collected AEFI reports including serious AEFIs that accounted for the majority of reports received in central database in 2010. The incidence rate of AEFI cases was 122 per million. A follow-up active surveillance through pregnancy exposure registries is ongoing to further evaluate the safety of vaccines in pregnant women.

120 WHO, UNICEF, World Bank. 2009. State of the World's Vaccines and Immunization, 3rd ed. http://www.who.int/immunization/sowvi/en/

121 WHO. 2010. New Database for WHO Prequalified Vaccines. Available at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html

122 UMC. Report from the WHO Collaborating Centre for International Drug Monitoring. 2009. Available at http://www.who-umc.org/graphics/21411.pdf

Box 8. Miscommunication on Vaccine Safety

Public trust is essential for vaccine programs. In Nigeria, the vaccination program met with resistance in some parts of the country because of suspicion of vaccines' safety and political situations. In 2003, local leaders in the states of Kano, Zamfara, and Kaduna advised parents not to allow their children to receive the polio vaccine, based on their suspicion that the vaccine could be contaminated with anti-fertility agents, carcinogen, and HIV. Local leaders accepted vaccination a year later only after identifying a vaccine manufacturer in Indonesia they could trust. It is claimed that part of the reason for the suspicion of western medicines might be the 1996 Pfizer trovafloxacine trial which a Nigerian panel called an "illegal trial of an unregistered drug."

Nigeria had polio recurrences in 2004 and 2007, which were attributed to poor media coverage and political elections. Though polio cases fell by 95% in 2009 and 2010, there is a current resurgence in 2011 with 30 polio cases reported in six northern states. It is not clear if the suspicion of the safety of vaccines has contributed in any way to this current resurgence. Nigeria's recurring cases have been linked to the global polio outbreaks, accounting for over 80% of the global polio burden in 2006. Clearly, there is a need to improve communication and provide more evidence-based information about vaccine safety to the public.

the existing vaccine safety infrastructure in developing countries and further develop a strategic plan for enhancing global vaccine safety activities. The stakeholders meeting to share situational analysis findings in resource-limited settings, conducted by the Brighton Collaboration, proposed an approach to strengthening vaccine PV by ensuring minimum capacity for PV at the country level, enhancing capacity where newly developed vaccines are introduced such as incorporating active surveillance, and strengthening international collaboration among all stakeholders.[123] The Brighton Collaboration also recently conducted a study on the capacity and needs of post-marketing vaccine safety monitoring in low- and middle-income countries. They concluded that there is a need to—

- Enhance vaccine safety monitoring
- Improve verification of safety concerns based on international standards
- Improve the infrastructure and analytical capacity for investigation of concerns
- Promote information sharing between national organizations and across countries
- Establish mechanisms and methods for risk communication
- Establish training programs and shared tools[79]

Other PHPs can learn lessons from the global and in-country immunization programs' experiences in improving vaccine safety monitoring.

Patient Safety and PV

In health facilities, the DTCs or Pharmacy and Therapeutics Committees can ensure provision of cost-effective quality care to patients. The committee is responsible for adapting, developing, and implementing an efficient and cost-effective formulary and for monitoring all medicines prescribed and dispensed to patients to ensure that they are safe and of good quality. However, the functioning of these committees is suboptimal, and issues with safe and appropriate use of medicines at health facilities abound as shown by the results of the following situational analysis.

123 WHO, the Global Vaccine Safety Blueprint Project. Available at http://www.who.int/immunization_safety/activities/GVS_blueprint_project/en/index.html

31 percent of 54 DTCs sampled in eight countries did not have any meetings in 2010 and most of the DTCs surveyed did not monitor and investigate medicine-related issues

In hospitals responding to the Patient Safety Situational Analysis, developed by the WHO African Partnerships for Patient Safety, the majority of hospitals surveyed indicated that they adopted their country's National Essential Medicine List as the hospital formulary. All hospitals surveyed stated that the majority of medicine was procured through the trusted national supply chain and was not subsequently tested. For outpatient medicines prescribed or for those medicines not available through the hospital pharmacy, direct purchase by patients or family members was required. Those directly purchasing medicines from local pharmacies stated that they sought the cheapest price possible, with few exceptions. Hospitals surveyed stated that patients were generally unaware of exact risks of counterfeits. The overwhelming majority did not chose medicine by brand or product origin, but chose by nearness of location to home or hospital setting and/or price. In all hospitals, the efficacy of these medications was not verified, even if they were brought into the hospital for dispensing to inpatients by the nurse. In addition, in a few hospitals, forms for the documentation of medication errors were supplied by external organizations conducting studies; however, these were not used or at least not collected by the hospital administration (to consider investigation or change) because it was not clear to whom they should go for follow up.[124]

Significant impact on preventing and managing medicines-related problems in patients can be made by DTCs through (1) monitoring and addressing medication errors, (2) ensuring medicine quality, and (3) monitoring and addressing ADRs.[125]

However, the finding shows that DTCs' abilities to ensure medicine safety in health facilities are weak. The assessment aimed to sample functioning DTCs;[126] however, 31 percent of 54 DTCs sampled in eight countries did not have any meetings in 2010 or were recently created (figure 30). DTCs in francophone countries were mostly inactive (60 percent in Burkina Faso, 67 percent in Senegal).

Most of the DTCs surveyed in the eight countries did not monitor and investigate medicine-related issues in 2010. Figure 31 shows the percentage of DTCs from selected countries that conducted drug use studies, medication error studies, product quality surveys, and active surveillance. Health facilities that undertook active surveillance activities were mostly sentinel sites participating in a study in collaboration with national PV centers. The extent of DTCs' involvement in addressing medicine safety and reviewing ADR reports varied across the countries (none in Senegal to 86 percent in Kenya; figure 32).

Some DTCs reported that they had reviewed and discussed ADR reports and safety information during their meetings and subsequently changed the formulary and standard treatment guidelines. For example, DTCs in Kenya removed stavudine from the formulary after reviewing the increased occurrence of stavudine-associated ADRs and recommendations from the national authority. One DTC in a regional hospital in Uganda regularly reviewed the safety profile of high-risk medicines and informed health care workers to closely monitor the toxicity of nevirapine after an extensive review of its safety profile. However, most DTCs do not regularly review ADR reports and inform health care workers of medicine safety issues. Training health care workers

124 Unpublished report from: Hospital Patient Safety in Africa: A Situational Analysis Synthesis from Six APPS Hospitals, WHO Patient Safety Feb 2010 and Hospital Patient Safety in Africa: Situational Analysis Revisited: A Comparison Report, WHO Patient Safety July 2011

125 Green, T. and K. Holloway. 2003. Drug and Therapeutic Committees: A Practical Guide. Geneva: WHO. http://apps.who.int/medicinedocs/en/d/Js4882e/

126 54 DTCs were sampled by convenient sampling methods in 8 countries: 5 in Burkina Faso, 5 in DRC, 14 in Ghana, 7 in Nigeria, 7 in Kenya, 6 in Senegal, 6 in Tanzania, and 4 in Uganda.

and educating the public to promote ADR monitoring and reporting was carried out in up to half of the sampled DTCs in eight countries.

DTCs have a critical role in implementing PV in health facilities. DTCs in Africa should be more actively engaged in PV-related activities by encouraging ADR reporting,

Figure 30. Functioning DTCs

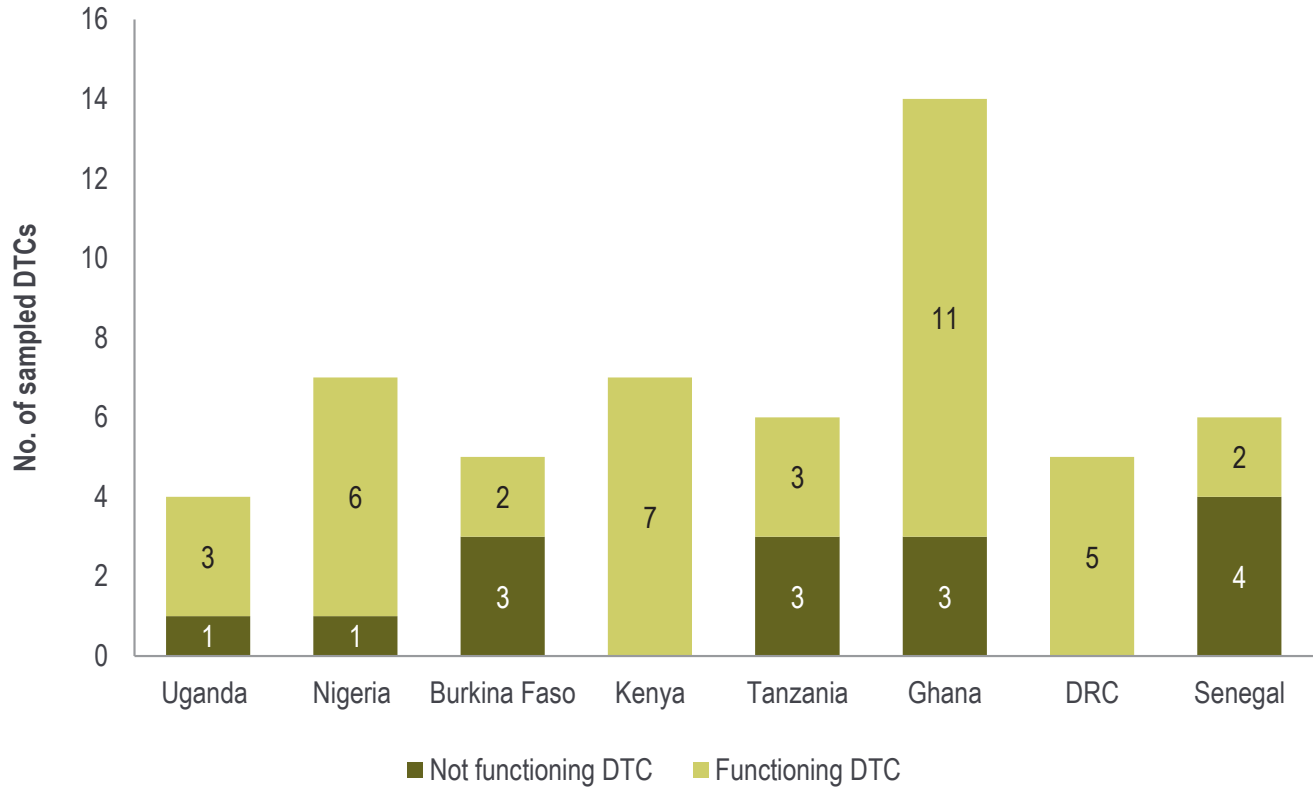


Figure 31. DTCs with drug use studies, medication error studies, product quality surveys, and active surveillance

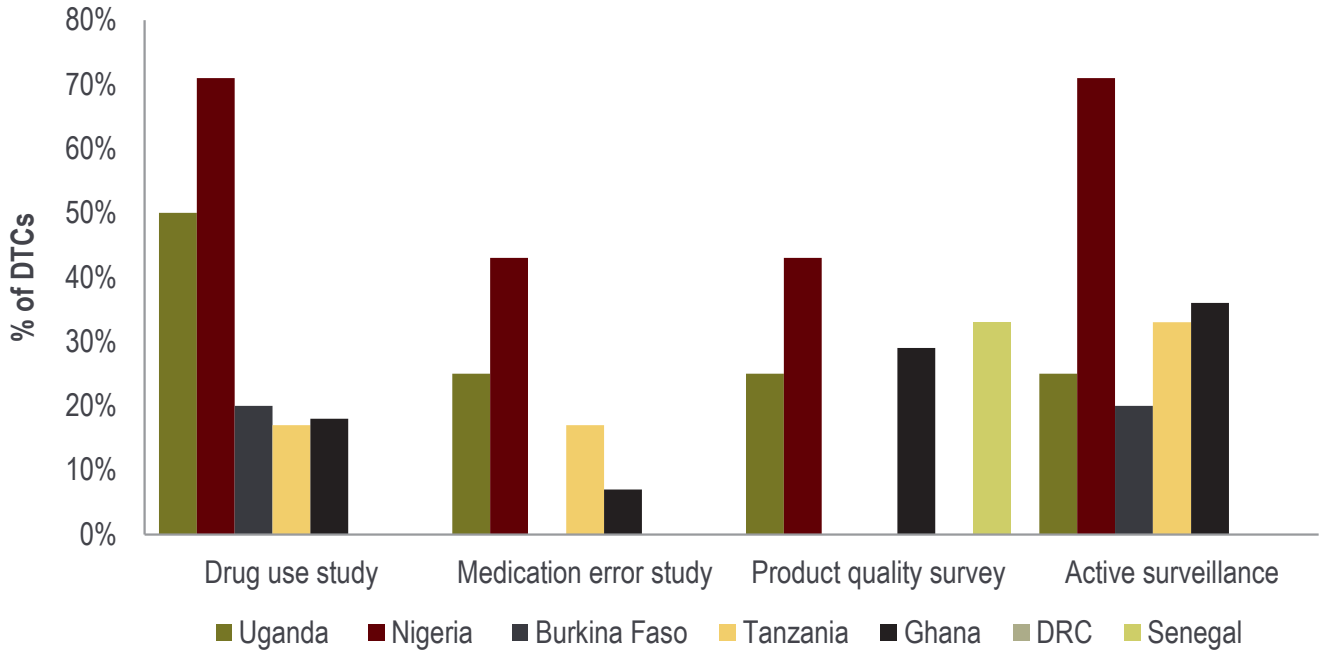
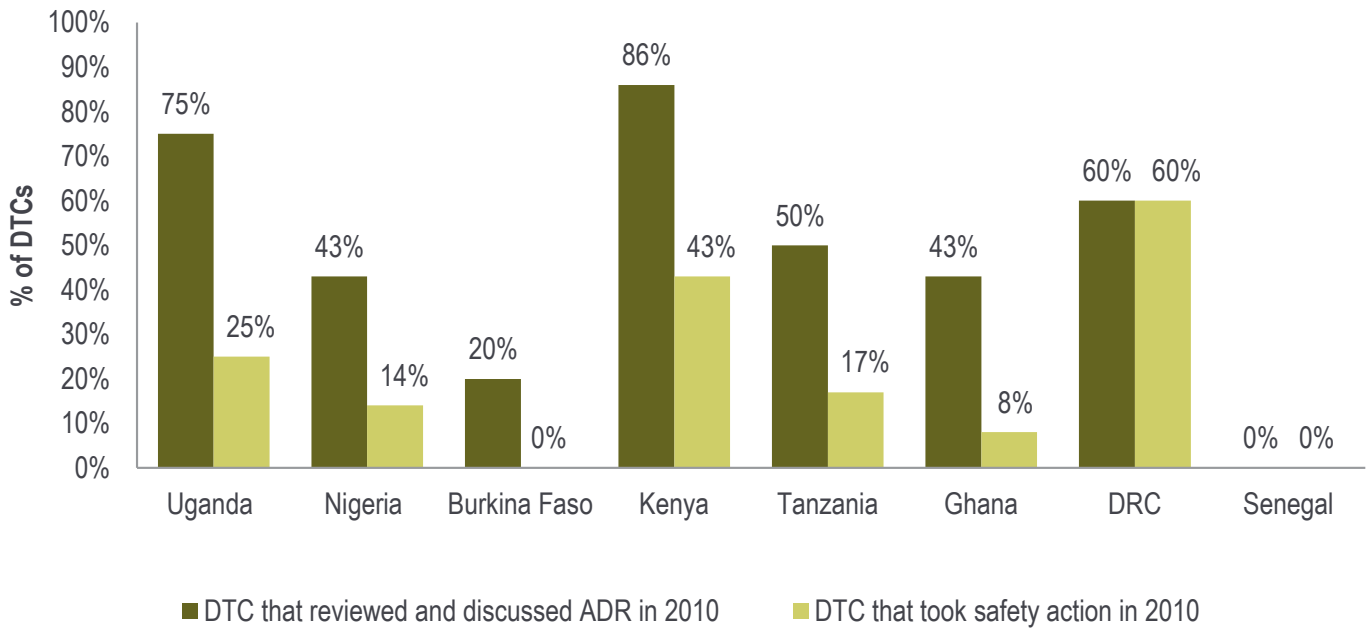


Figure 32. DTCs with PV activities



identifying high-risk drugs on formularies and closely monitoring use, regularly reviewing ADR reports and safety information, investigating medicine use and medication errors, and adapting formularies or STGs to reflect newly identified issues.

PV in Pharmaceutical Industry

Most multinational companies report ADRs to their own global database and follow their own SOPs without giving that information to NMRA.

The MAHs must establish an appropriate PV system to assure responsibility and liability for their products, and they should also monitor and report adverse events related to the use of their products wherever the product is marketed. SRAs such as the FDA and EMA require MAHs to report ADRs that occur in all countries where their products are marketed and conduct post-marketing safety studies or risk minimization activities for high-risk medicines and products with unresolved safety concerns,[127,128] according to ICH guidelines.[63] In SSA, only 13 (28 percent) countries have legal provisions that require MAHs to report all serious ADRs to the NMRA and 8 countries (17 percent) require MAHs to conduct post-marketing surveillance activities. The lack of a legal mandate to regulate the industry for medicine safety led to minimal or no involvement of the pharmaceutical industry in PV.

We surveyed 21 pharmaceutical companies in 7 countries including 10 multinational innovator companies (MICs), 4 multinational generic companies (MGCs), and 7 locally owned companies (LOCs) (table 10).[129] Only 8 (38 percent) of these companies have a unit or staff responsible for PV activities and 5 (24 percent) have an SOP or reporting forms for PV. Very few companies (14 percent of these companies) conduct

127 FDA. Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccine. 2001. Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm

128 European Union. Legislation Volume 9: Guidelines for Pharmacovigilance for Medicinal Products for Human and Veterinary Use. Available at http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9_10-2004_en.pdf

129 Burkina Faso (3), DRC (1), Ghana (2), Kenya (4), Nigeria (5), Tanzania (3), Uganda (3).

Table 10. Pharmaceutical Companies Surveyed

	Number of companies surveyed		
	MIC	MGC	LOC
Burkina Faso	2	1	0
DRC	0	0	1
Ghana	2	0	0
Kenya	2	1	1
Nigeria	2	1	2
Tanzania	1	0	2
Uganda	1	1	1
Total	10	4	7

Table 11. PV Activities in Pharmaceutical Companies

Number of companies surveyed	MIC (10)	MGC (4)	LOC (7)	Total (21)
With PV unit or staff	6	1	1	8
With SOP or reporting form	4	0	1	5
That have sent ADR reports to regulatory authority in 2010	3	0	0	3
That have carried out post-marketing surveillance in 2010	2	0	1	3

post-marketing surveillance activities. The situation was even worse in the context of local manufacturers and companies manufacturing generics because of the perception that monitoring ADRs is not relevant for generics with well-known safety profiles. Table 11 shows the kinds of companies (e.g., MICs, MGCs, and LOCs, etc.) that participate in PV activities. In Uganda, Kenya, Ghana, and Tanzania where there is no such regulation, almost none of the pharmaceutical companies surveyed (except those in Kenya) had a basic structure (such as a responsible unit or SOP for PV) or carried out PV-related activities. Most of companies studied in Nigeria have structures to carry out PV activities; however, companies' actual PV activities were rarely observed. Awareness of national PV guidelines, regulations, or the ADR form was very low.

Most multinational companies report ADRs to their own global database and follow their own SOPs without giving that same information to national regulatory authorities. Most companies didn't have a quality monitoring system in place; only three companies confirmed that they tested samples when they received complaints concerning the product quality. Another study is required to further assess quality assurance systems of the SSA pharmaceutical industry. The pharmaceutical industry needs to be informed about national PV guidelines and its responsibility to ensure the safety and quality of products; the industry should be encouraged to conduct PV activities in close collaboration with national regulatory authorities.

South Africa has the strongest pharmaceutical industry among SSA countries, accounting for almost 70 percent of the total SSA's pharmaceutical market. To obtain a more complete view, we conducted a comprehensive assessment of 25 South African pharmaceutical companies (covering 25 percent of the current industry).

South Africa's results provide the best possible scenario of pharmaceutical industry PV among SSA countries. Although the result shows some encouraging trends of PV development in South African industry regarding structure and process for ADR reporting, gaps exist in data collation, risk evaluation, and decision making (see section Pharmacovigilance Systems in selected countries: South Africa).

Capacity of PV Systems in SSA

A comprehensive PV system is comprised of (1) policy, law, and regulation; (2) system structure and stakeholder coordination; (3) signal generation and data management; (4) risk assessment and evaluation; and (5) risk management and communication.

Table 12. Measurement of PV Systems Capacity Classified in Groups

PV component	Indicators[a]	Systems classification			
		Group 1	Group 2	Group 3	Group 4
Policy, law, and regulation	**Policy statements for PV or medicine safety exist** **Legal provision for PV exists** Legal provision for MAHs to report all serious ADRs exists Legal provision for MAHs to conduct post-marketing safety activities exists	N	Y	Y	Y
System, structure, and stakeholder coordination	**PV center or unit with a clear mandate, structure, roles, and responsibilities exists** **Drug information service that provides safety information exists** **National PV guideline or SOPs exists** **National medicine safety advisory committee exists** **Strategy or platform to coordinate PV activities across all stakeholders exists** Membership in the WHO Programme for International Drug Monitoring	N	Y	Y	Y
Signal generation and data management	**Existence of a system (or a database) for collating PV information from all sources (ADR reports, PSURs, AEFI reports, reports from PHPs, active surveillance safety reports, reports from clinical trials)** **Scope of PV includes product quality, medication errors, treatment failure, and ADRs (2 points each)**	N	N	Y	Y
Risk assessment and evaluation	**Number of ADR reports (more than 100 per million population)** **Number of active surveillance activities in the last 5 years (more than 1)** Number of product quality surveys carried out in the last 5 years (more than 1) Number of medication error surveys/drug use studies carried out in 2010 (more than 1) Capacity to conduct safety research and clinical trials exists	N	N	Y	Y
Risk management and communication (outcome indicators)	Percent of planned issues of safety newsletter/bulletin published in 2010 (more than 50%) Number of safety alerts developed and distributed (more than 70% of locally relevant safety alerts from international sources) **Number of actions taken as a result of PV activities (more than 1)**	N	N	N	Y

[a]Core indicators (in **bold**) are equal to 2 points each, the rest (supplementary) are equal to 1 point each. When the score of indicators met/total score of indicators (×100) is >60 percent for each component, the country is said to meet the standard requirements for that component.

Using a set of indicators[130] addressing all of these components, SPS developed criteria for classification of countries into four groups. Table 12 lists the criteria for classification into these groups, otherwise called the systems classification.

The systems classification indicates that only four countries have a complete set of essential components of a comprehensive PV system.

The scoring of the classification scheme is as follows: core indicators are given 2 points each and the rest of the indicators are given 1 point each. The score of the indicators met is divided by the total score of all the indicators and multiplied by 100; if this value is > 60 percent for each component, the country is said to meet the standard requirements for that component. Country-specific data for all indicators can be found in annex A. The groupings represent the level of achievement of countries with regard to meeting the relevant indicators in the components of a PV system.

WHO defined the minimum requirements for a functional national PV system as having a national PV center, a spontaneous reporting system, a national database, a national PV advisory committee, and a communications strategy.[131] According to a presentation made by WHO, countries were classified into four groups depending on PV capacity.[132] The systems classification SPS developed builds on this and further highlights the need for relevant policy and legislation as well as the systems, structures, and stakeholder coordination that are the foundation for sustainable PV activities. It also considers various elements related to systems' performance, such as the capacity to minimize and prevent medicines-related harm in patients by generating signals, evaluating risks, and managing the risks effectively. The systems classification complements the WHO minimum requirements by providing further details and indicators for monitoring all aspects of comprehensive PV systems and for verifying and benchmarking systems performance. Using the systems classification, we classified countries into four groups based on the study findings related to the capacity and performance of their PV systems.

- **Group 1—Countries with minimal or no capacity for PV.** There are no legal or structural frameworks for PV systems and no coordinated passive or active surveillance in these countries. Any ongoing PV activities (e.g., collecting ADR data in a few hospitals or programs) take place without national coordination. Most countries that had not joined the WHO program would fall under this group (24 countries—Angola, Benin, Burkina Faso, Burundi, Cameroon, Cape Verde, Gambia, Guinea-Bissau, Liberia, Madagascar, Mauritius, Niger, Sudan, and all non-members of the WHO program except Malawi).
- **Group 2—Countries with basic structures in place.** The countries have policy and legal frameworks for PV. Most basic organizational structures, such as an institution with a clear mandate for PV, guidelines and SOPs, a reporting form, and a safety advisory committee, are in place. Roles and responsibilities of stakeholders are recognized, but not fully coordinated. The capacity to generate signals and evaluate the risks is limited in these countries without functioning spontaneous reporting programs covering the full scope of PV, and without active approaches to

130 It is a set of 23 indicators comprising 15 core and 8 supplementary indicators adapted from IPAT indicators. Every indicator has a benchmark for its measurement.

131 WHO. Minimum Requirements for a Functional Pharmacovigilance System. 2010. Available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/PV_Minimum_Requirements_2010_2.pdf

132 Group 1 (may have an office or a person, a reporting form, but minimal or no activity): Cameroon, Ethiopia, Kenya, Senegal, Sudan, Zambia, and all other African countries; group 2 (data are gathered): Mozambique, Sierra Leone, Uganda, Madagascar, Togo; group 3 (data are gathered, analyzed, and shared): Namibia, Tanzania, Zimbabwe; group 4 (data are gathered, analyzed, shared, and processed into policy): South Africa, Nigeria, Ghana. From presentation at ASTMH 2009 Symposium, current status of PV in Africa (UMC analysis)

evaluate signals and implement effective risk management practices (15 countries—Botswana, Cote d'Ivoire, DRC, Ethiopia, Mali, Rwanda, Togo, Zambia, Zimbabwe, Kenya, Senegal, Malawi, Mozambique, Guinea, and Sierra Leone).

- **Group 3—Countries with capacity to collect and evaluate safety data on the basis of legal and organizational structure.** Countries in this group have organizational structure and policy framework to collect safety data, collate them in a national database, and evaluate the risks and benefits by both passive and active approaches. However, the capacity to manage the risks by taking appropriate actions, develop a plan to actively monitor the risks, and communicate with stakeholders is lacking (2 countries—Tanzania, Ghana).
- **Group 4—Countries with performing PV systems that detect, evaluate, and prevent medicine safety issues.** These countries have the basic structures, both passive and active surveillance activities, and the capacity to evaluate the risks. Based on these, outcomes of PV activities inform regulatory actions and are communicated to stakeholders. Countries in this group do not necessarily reflect a perfect or ideal PV system. It is unclear if the current situation will be sustained over time (4 countries—South Africa, Namibia, Nigeria, and Uganda).

Most countries fall under groups 1 and 2 (87 percent); 25 countries including nonmembers of the WHO program belong to group 1; and 15 and 2 countries belong to groups 2 and 3 respectively, while 4 countries belong to group 4 (figure 33). All associate members were either in group 1 or 2. According to the recent WHO World

Figure 33. PV systems' capacity in SSA countries

Medicines situation report on PV,[133] the number of SSA countries with functional PV centers has increased substantially, from under 10 in 2000 to well over 20 countries by 2010. However, this study's systems classification indicates that only 4 countries have performing PV systems to detect, evaluate, and prevent medicine safety issues with a complete set of essential components of a comprehensive PV system.

This classification is limited by our inability to conduct in-depth assessment in all countries. Such assessments conducted by skilled PV consultants would have the highest potential for truly ascertaining and verifying PV systems' performance. Besides the countries where in-depth assessment was conducted, there was no way to verify the data obtained through the surveys or literature. The indicators with a benchmark or a threshold for computation were not validated for their sensitivity and specificity. For example, a threshold of 100 reports per million per year was used to compute the indicator number of ADR reports received in 2010 because it is a lower and more attainable threshold than 200 reports per million per year recommended by WHO/Uppsala Monitoring Centre (UMC).[134]

PV Development and Its Associated Factors

The relationship between PV capacity and various factors, such as socioeconomic factors, health system development, pharmaceutical industry development, regulatory capacity of national authority, languages, regional location, and the year of becoming a member of the WHO program, was reviewed to understand contributing factors to PV development (tables 13 and 14 and figure 34). No conclusive evidence or trend was found in this analysis to establish the association between PV capacity and any of these factors. It was noted that countries with the most complete set of components of a comprehensive PV system happen to be anglophone countries (tables 15 and 16). Meanwhile, all francophone and lusophone countries belong to group 1 or 2. Even though the current study didn't observe any direct association between the factors and PV capacity, these factors including pharmaceutical market size and regulatory capacity might have implications to the development of PV systems. Several studies that assessed regulatory capacity of African countries support this assumption. A WHO study in 2004 showed that 90 percent of African NMRAs lacked regulatory capacity to ensure the quality, efficacy, and safety of medicines in their country.[135] Another WHO report on vaccine regulatory issues concluded that South Africa had a fully functional NMRA and Nigeria and Uganda had either functional or potential NMRAs, who all belong to group 4.[136] The recent report on the assessment of 26 NMRAs in SSA stated that only four NMRAs have all elements of regulatory functions. However, further study might be required to investigate what has substantially contributed to the development of PV systems capacity.

Countries with the most complete set of components of a PV system happen to be anglophone

133 Pal, S., A. Dodoo, A. Mantel, S. Olsson. WHO. 2011. World Medicines Situation 2011: Pharmacovigilance and Safety of Medicines. Available at http://apps.who.int/medicinedocs/documents/s18771en/s18771en.pdf

134 The Uppsala Monitoring Centre (UMC). Reporting Trends. Available at http://who-umc.org/DynPage.aspx?id=108476&mn1=7347&mn2=7252&mn3=7322&mn4=7558

135 WHO. Medicines Regulatory Authorities: Current Status and the Way Forward. Regional Committee for Africa. AFR/RC56/11. June 2006.

136 Belgharbi, L. Vaccine Regulatory Issues in African Countries: Building and Sustaining National Capacity. EDCTP consultative meeting, June 2007. Available at http://www.edctp.org/fileadmin/documents/Regulatory_meeting_Lahouari_Belgharbi.pdf

Table 13. PV Capacity and its Associated Factors

	Group 1	Group 2	Group 3[a]	Group 4
GDP per capita (USD, 2010)[b]	189-20,200 (median 1023)	194-7,513 (median 570)	527-1,287 (median 907)	503-7,280 (median 3363)
Population (million, 2010)[c]	0.1-41 (median 3)	2-81 (median 13)	23-43 (median 33)	2-151 (median 40)
Health expenditure per capita (USD, 2009)[d]	18-709 (median 52)	3-612 (median 42)	25-53 (median 39)	43-485 (median 164)
Health workforce per 10,000 population (2010)[e]	2-123 (median 10)	2-40 (median 6)	3-14 (median 9)	15-53 (median 29)
Pharmaceutical market size (USD million)[f]	2-183 (median 6)	2-173 (median 37)	80-120 (100)	93-2,514 (median 233)
No. of registered drugs[g]	2,400-5,000 (median 3,702)	280-4,608 (median 2850)	2,490-4,713 (median 3602)	3,646-12,083 (median 5243)

Note: This descriptive analysis does not provide any conclusive evidence to establish an association between PV capacity and any of these factors.

[a]Presents data from only two countries in group 3

[b]GDP per capita, World Bank 2010

[c]Population, World Health Statistics, 2010

[d]Total expenditure on health per capita, WHO National Health Account Database 2009

[e]Health workforce is the total number of physicians, nurses, midwives, dental and pharmaceutical personnel, and public health and community health workers; WHO World Health Statistics 2011

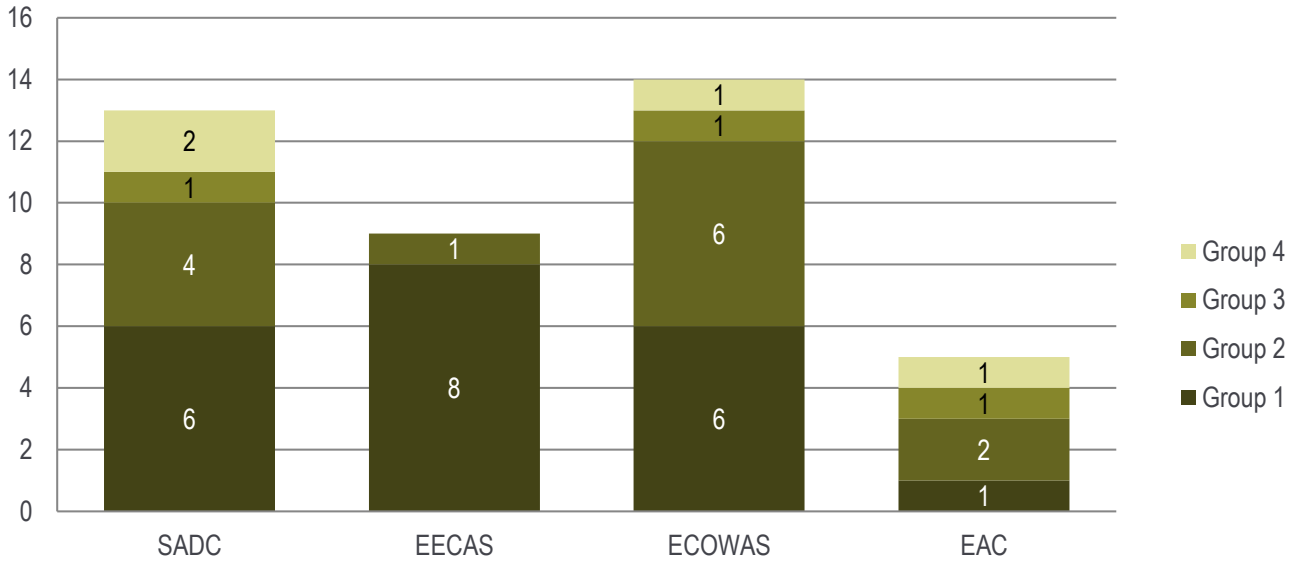
[f]Pharmaceutical market size was estimated from total pharmaceutical consumption: local production of pharmaceuticals + imported pharmaceuticals − exported pharmaceuticals; source: UN Commodity Trade Statistics 2006 and IFC pharmaceutical market size 2006

[g]Number of registered drugs from WHO pharmaceutical country profile and regulatory agency's website

Table 14. PV Capacity and Year of Becoming a Member of the WHO Program

	Year of becoming a member of the WHO program		
	~2000	2001-2005	2006-2011
Group 1	0	0	4
Group 2	1	1	11
Group 3	1	1	0
Group 4	1	1	2

Figure 34. PV capacity in four regions



Note: SADC, Southern African Development Community; ECOWAS, Economic Community of West African States; EAC, East African Community; EECCAS, Economic Community of Central African States

Table 15. Anglo/Franco/Lusophone Countries in Each Group

	Group 1	Group 2	Group 3	Group 4
Anglophone	5	7	2	4
Francophone	16	7	0	0
Lusophone	4	1	0	0

Table 16. Socioeconomic and Health Development Characteristics for Different Language Groups

Health development characteristics	Anglophone	Francophone	Lusophone
GDP per capita (USD, 2010)[a]	13-7,513 (median 648)	189-20,200 (median 690)	410-4,443 (median 1190)
Population (million, 2010)[b]	1-151 (median 28)	0.1-64 (median 9)	0.2-22 (median 2)
Health expenditure per capita (USD, 2009)[c]	15-612 (median 60)	3-709 (median 38)	18-204 (median 91)
Health work force per 10,000 population (2010)[d]	3-103 (median 14)	2-123 (median 9)	4-36 (median 22)
Pharmaceutical market size (USD million)[e]	2-2,514 (median 69)	2-159 (median 19)	2-49 (median 2.3)

[a]GDP per capita, World Bank 2010

[b]Population, World Health Statistics, 2010

[c]Total expenditure on health per capita, WHO National Health Account Database 2009

[d]Health workforce is total number of physicians, nurses, midwives, dental and pharmaceutical personnel, and public health and community health workers; WHO World Health Statistics 2011

[e]Pharmaceutical market size was estimated from total pharmaceutical consumption: local production of pharmaceuticals + imported pharmaceuticals − exported pharmaceuticals; source: UN Commodity Trade Statistics 2006 and IFC pharmaceutical market size 2006

Global Initiatives for Strengthening Pharmacovigilance Systems

A broad range of international and local stakeholders are working towards strengthening PV and ensuring medicine safety in Africa (annex B). It is important to coordinate these on-going efforts and bring the limited resources together. In particular, where various players and initiatives are supporting countries' PV activities, effective coordination should be sought to ensure these efforts are complementary and targeted specific needs that will ultimately lead to strengthening the national PV system.

Financing Institutions

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The Global Fund supports strengthening PV systems in countries as a component of grant activities. For example, the R10 proposal called for countries to include PV in proposals and, if necessary, to request funding for PV. The Global Fund's Affordable Medicines Facility–malaria (AMFm) is a financing mechanism to expand access to ACTs that also provides support on PV in seven African countries—Ghana, Kenya, Madagascar, Tanzania, Niger, Nigeria, and Uganda. It defines PV as a main area of intervention to support the successful and sustainable implementation of AMFm.[137] However, it is unknown as to what extent PV activities have been implemented in countries with the Global Fund's financial support.

A WHO-Global Fund PV stakeholders' meeting was held to review a PV strategy[75] and toolkit in November 2010 in Accra, Ghana. The strategy suggests a comprehensive and sustainable partnership for national PV system strengthening. The PV toolkit developed by UMC-Africa was presented for further comments and review. Four work streams—technical, advocacy, financing, and partnership—were identified, and roles and responsibilities of each institution under these streams were discussed.

137 The Global Fund. Application form: Affordable Medicines Facility–malaria (AMFm) Phase 1, 2009

Where various players are supporting countries' PV activities, effective coordination should be sought to ensure these efforts are complementary.

USAID through USAID-funded SPS, SIAPS, and PQM programs

USAID supports countries to strengthen medicines safety and quality monitoring system by funding PV activities in PEPFAR and PMI programs in developing countries. The agency also supports SPS and Systems for Improved Access to Pharmaceuticals and Services (SIAPS) programs of MSH and the USP/PQM program to help implement PEPFAR and PMI activities and work with countries to assure the availability of safe and quality pharmaceuticals and effective pharmaceutical services under the Global Health Initiative principles.

The Bill & Melinda Gates Foundation

The BMGF sponsored a four-year project to improve PV in HIV/AIDS programs in six countries. In Tanzania, six sentinel sites were established for CEM for ARVs. In Kenya, spontaneous reporting has been evaluated by partnership between Moi University (Eldoret, Kenya) and the Consortium of Universities.[138] BMGF also provided support for the collaborative work between the US National Institute of Allergy and Infectious Diseases and WHO to establish spontaneous adverse event reporting in two countries[139] and the WHO-initiated project, the Global Network for Post-Marketing Surveillance of Newly Prequalified Vaccines—the PMS Network.[140]

European Commission

The European Commission, under the Seventh Framework Programme,[141] has supported the Monitoring Medicines project in collaboration with WHO and UMC for three and a half years. The project is being implemented in 11 countries including some in Africa.[142,143] The project focuses on strengthening consumer reporting, supporting countries to expand the scope of PV, promoting better and broader use of existing PV data, and developing active and focused surveillance methods.

UNITAID

UNITAID is an international facility for purchasing HIV/AIDS, malaria, and TB medicines. It supports WHO's work to develop norms and standards in PV and prequalification of some medicines.

GAVI Alliance

Since 2000, the GAVI Alliance has provided support to increase vaccination coverage. The Yellow Fever Initiative (2006-2013) with preventative mass vaccination campaigns is distributing vaccines in 12 West and Central African countries; the urgency of establishing functional PV systems was addressed to ensure the safety of vaccination. As

138 Duncombe, Chris. November 2010. Priorities and Initiatives to Advance Pharmacovigilance in HIV Program; presentation at WHO/GF stakeholder's meeting, Accra, Ghana.

139 Lalvani, P. and J. Milstein. 2011. Access to New Health Products in Low-Income Countries and the Challenges of Pharmacovigilance. TB Alliance. Available at http://www.oneworldhealth.org/pdf/PharmacovigilanceDiscussionPaper.pdf

140 UMC. 2009. Uppsala Reports 46: Global Network for Vaccines Safety. Available at http://who-umc.org/graphics/24354.pdf

141 European Commission. FP7: The Future of European Union Research Policy. July 2010. Available at http://ec.europa.eu/research/fp7/index_en.cfm

142 WHO. Recommendations from 8th Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ASCoMP), Geneva, March-April 2011. Available at http://www.who.int/medicines/areas/quality_safety/safety_efficacy/recommendations.pdf

143 Monitoring Medicines website. Available at http://www.monitoringmedicines.org

a condition of funding, the GAVI Alliance requires that an AEFI surveillance system be implemented. To address this requirement, Agence de Médecine Préventive and WHO have provided technical support, including developing surveillance tools, introducing active case finding methods, and creating and training national expert committees to review and classify suspected serious AEFIs.[144] In addition, GAVI, in collaboration with the WHO Regional Office for South-East Asia, made funds available for supporting countries to establish national AEFI committees and train their members.[145]

Technical Institutions and Partnership Programs

World Health Organization

WHO provides norms and standards on PV-related activities. Several departments such as Essential Medicines and Pharmaceutical Policies and the HIV department work across the issues related to PV. It also hosts the WHO Advisory Committee on Safety of Medicinal Products. The committee, composed of members from WHO expert advisory panels for drug evaluation and for drug policies and management, focuses on providing advice on safety issues related to PV. The Immunization, Vaccines, and Biologicals Department initiated the Global Network for Post-Surveillance of Newly Prequalified Vaccines to establish standardized, post-marketing safety surveillance of vaccines that are newly prequalified and introduced or those vaccines that are being used more widely in 11 countries, including Senegal and Uganda.

The Uppsala Monitoring Centre

As a WHO Collaborating Centre, UMC manages the WHO Programme for International Drug Monitoring. It supports PV activities in 104 official member countries and 35 associate members, reviews the ADR reports submitted to the WHO program to identify a new signal, and provides training and communications courses for health care professionals. UMC developed and maintains VigiFlow, a web-based individual case safety report management system designed for use by national centers, and CemFlow®, a data management tool for CEM programs. Others include a tool that searches all case reports (VisiSearch®), a statistical tool (VigiMine®), a system to monitor adverse events following H1N1 vaccines (PaniFlow®), the WHO Drug Dictionary, and WHO-Adverse Reaction Terminology.[146]

International Society of Pharmacovigilance

The International Society of Pharmacovigilance fosters PV in scientific and educational perspectives and enhances the safe and proper use of medicines. It encourages research and education at all levels, promotes a regular exchange of information, and engages in other activities related to PV. It hosts annual meetings and training courses on a broad range of topics, including causality assessment, risk management, mechanisms of ADRs, and regulatory inspections.[147]

144 Breugelmans, G. J. and B. Gessner. Surveillance of Serious Adverse Events Following Immunization in Resource Poor Settings. Biomed Central Proceedings; 5(Suppl 1): P32.
145 WHO. 2011. Adverse Events Following Immunization in the South-East Asia Region 2008-2010. http://203.90.70.117/PDS_DOCS/B4670.pdf
146 UMC website. available at http://www.who-umc.org/DynPage.aspx?id=97218&mn1=7347&mn2=7252
147 ISOP website. Available at http://www.isoponline.org/

Council for International Organizations of Medical Sciences

The Council for International Organizations of Medical Sciences, established jointly by WHO and UNESCO in 1949, is representative of the biomedical scientific community, including biomedical disciplines, national academies of sciences, and medical research councils. Activities related to PV include developing quantitative methods for signal detection with a PV database, establishing vaccine PV, and developing a risk minimization toolkit—a set of tools and guidelines for managing risks of medicinal products in collaboration with regulatory agencies, the pharmaceutical industry, government institutions, and academia.[148]

ICH

The ICH was established by regulatory authorities and industries of Europe, Japan, and the United States to harmonize technical guidelines and requirements of drug registration. The ICH module E1 to E2F guidelines on clinical safety address several PV topics including expedited reporting, individual case safety reports, PSURs, and PV planning.[149]

Brighton Collaboration

The Brighton Collaboration is a global research institution to facilitate the development, evaluation, and dissemination of vaccine safety information. Its activities include providing definitions and guidelines for AEFI, promoting collaborative vaccine safety studies, linking study data, and building vaccine safety monitoring capacity. It supports the BMGF-funded Global Vaccine Safety Blueprint project by assessing needs and identifying possible minimum capacity requirements of regulatory authorities in low- and middle-income countries to monitor and ensure the safe use of vaccines.[150]

Management Sciences for Health

MSH is a not-for-profit technical assistance and project management organization that works to strengthen health systems. It has supported the implementation of PV activities through the USAID-funded SPS program and a new, five-year USAID-funded SIAPS[151] program, by training national staff, developing training materials, guidelines and tools, establishing organizational structures, reviewing PV regulations, and using PV data for taking regulatory decisions or updating relevant policies and guidelines. The SPS program has supported PV systems strengthening in 10 countries—DRC, Kenya, Rwanda, Ethiopia, Ghana, Namibia, South Africa, Nigeria, India, and Vietnam.

US Pharmacopeia

USP is a nonprofit public health organization that sets standards for the quality, purity, identity, and strength of medicines, food ingredients, and dietary supplements manufactured, distributed, and consumed worldwide. USP's drug standards are enforced by US FDA, and these standards are developed and relied upon in more

148 CIOMS website. Available at http://www.cioms.ch/index.html
149 ICH website. http://www.ich.org/
150 Brighton Collaboration website, available at https://brightoncollaboration.org/public/what-we-do/capacity.html
151 SIAPS is a new, USAID-funded five-year program that will build on the achievements of its predecessor (SPS program) by working to assure the availability of quality pharmaceutical products and effective pharmaceutical services to achieve desired health outcomes.

than 130 countries. Since 1992, USP has worked to help developing countries address critical issues related to poor-quality medicines and their appropriate use through USAID-awarded DQI and PQM programs. The PQM serves as a mechanism to strengthen quality assurance and quality control systems and combat the availability of substandard and counterfeit medicines.[109] In the area of PV, the PQM program has supported countries, including Madagascar and Senegal, to establish national PV programs involving various national agencies for better and coordinated spontaneous reporting of ADEs.

Medicines for Malaria Venture

Medicines for Malaria Venture is a product development partnership established in 1999 to discover, develop, and facilitate delivery of new, effective, and affordable antimalarial drugs. It coordinates the full cycle of drug development—research, clinical trials, registration, and post-marketing surveillance. The on-going portfolios include several phase 4 studies of antimalarials in resource-limited settings.[152]

Médicins Sans Frontièrs

Médicins Sans Frontièrs (MSF) is an international, independent organization for medical humanitarian aid. Its treatment programs and cohort monitoring provide incidences of ADR and treatment failure data related to the use of ARVs and ACTs in resource-limited settings.[153,154] MSF and WHO are discussing integrating PV into MSF's Chagas disease program.[142]

International Epidemiologic Database to Evaluate AIDS

International Epidemiologic Database to Evaluate AIDS is a research institution that collects and harmonizes data from international research related to HIV/AIDS. It conducted pilot studies on the implementation of ADR reporting in an HIV cohort in Cote d'Ivoire.[12]

International Pharmaceutical Federation

The International Pharmaceutical Federation, the global federation of national pharmacists associations, stresses the key role of the pharmacist in PV—surveillance of the safe use of medicines, early detection of new ADRs in clinical settings, continuing education on the nature of safety of medicines, and promoting PV activities to consumers, prescribers, and relevant government institutions.[155]

Forum for Collaborative HIV Research

The Forum is a private–public partnership that addresses a range of global HIV/AIDS issues, including treatment-related toxicities, health services research, co-infections, and the transference of research results into care. It supported a meeting in 2010 involving key stakeholders to discuss the creation of a sustainable global PV system for ARVs.[57]

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152 Medicines for Malaria Venture website. http://www.mmv.org/research-development/science-portfolio

153 Bygrave, H., K. Kranzer, K. Hilderbrand, et al. 2011. Renal Safety of a Tenofovir-Containing First-Line Regimen: Experience from an Antiretroviral Cohort in Rural Lesotho. PLoS One 6(3): e17609

154 Ford, N. and A. Calmy. 2010. A. Improving First-Line Antiretroviral Therapy in Resource-Limited Settings. *Current Opinion* in *HIV* and *AIDS* 5(1):38-47.

155 International Pharmaceutical Federation. 2006. FIP Statement of Policy: The Role of the Pharmacist in Pharmacovigilance. Available at http://www.fip.org/www/uploads/database_file.php?id=273&table_id=

Drugs for Neglected Diseases Initiative

Drugs for Neglected Diseases Initiative is a drug research and development organization for neglected diseases established by the Oswaldo Cruz Foundation, Indian Council for Medical Research, Kenya Medical Research Institute, Ministry of Health of Malaysia, Pasteur Institute, MSF, and Research and Training in Tropical Disease.[156] Through the initiative and its partners, artesunate-amodiaquine and artesunate-mefloquine became widely available. To ensure safety and effectiveness of these products in real-life settings, Drugs for Neglected Diseases Initiative has implemented a long-running monitoring plan in close collaboration with its partners Sanofi-Aventis, Medicines for Malaria Venture, MSF, national PV centers, and national disease programs. As part of the monitoring plan, several proactive surveillance studies have been conducted in SSA including a two-year study in Cote d'Ivoire to evaluate clinical and biological safety of artesunate-amodiaquine in a population of 14,000.[157]

Disease-Oriented Partnership Programs

Disease-specific partnership programs include Roll Back Malaria (RBM) Partnership, Stop TB Partnership, PEPFAR, PMI, and Presidential Initiative for Neglected Tropical Diseases (NTD) have contributed to strengthen PV in countries by encouraging national counterparts or their implementing partners to integrate PV into the disease control programs and directly supporting PV activities. For example, the RBM issued a guideline for countries to include PV as a component of the National Malaria Plan and to include a PV budget in its proposal to the Global Fund (R8) and other donor programs.[158] The NTD established a mechanism to monitor SAEs and urged its implementing partners to adhere to the proper procedure for SAE reporting by reporting to drug donation programs, pharmaceutical companies, and local authorities.[159]

Regional Institutions and Region-Focused Disease Programs

One of the key values of a review and inventory of institutions that offer trainings in PV and related areas is to facilitate opportunities for linkages and collaborations across countries and regions. This section therefore provides a listing of institutions across the entire of Africa so as to inform all who may be interested in regional or supra-regional linkages that may be necessary because of commonalities in language and other demographics (table 17).

In-Country Institutions with PV Activities in Africa

Disease programs, research institutions, teaching hospitals, and local nongovernmental organizations that conduct safety research and phase 4 studies in Africa are listed in table 18. Figure 35 illustrates the collaboration between the local institutions and their sponsors for conducting medicine safety research or PV activities.

156 Drugs for Neglected Diseases Initiative website. Available at http://www.dndi.org/index.php

157 Bompart, F. Presentation at Malaria Symposium in 2008. Efficacy and Safety Monitoring in the Field: The Artesunate-Amodiaquine Fixed-Dose Combination Monitoring Plan. Access to Medicines, sanofi-aventis. Available at http://www.dndi.org/images/stories/events2008/asmth/1_bompart_s-a_astmh2008_final.pdf

158 http://www.rollbackmalaria.org/mmss/docs/PharmacovigilanceIntro-en.pdf

159 USAID. 2008. Stakeholders' Meeting: Presidential Initiative for Neglected Tropical Disease (NTD) Control. Working Paper 2: Drug Supply and Delivery: Provision of Essential Medicines for Preventative Chemotherapy for Neglected Tropical Diseases.http://www.usaid.gov/our_work/global_health/id/workingpaper2.pdf

Table 17. Regional Training Institutions in PV

Country/ region	Name of institution/ organization/collaboration	Functions/terms of reference/training areas
East Africa	Regional Technical Resource Collaboration for Pharmaceutical Management[a]—network of academic institutions from Uganda, Tanzania, Kenya and Rwanda	Conduct assessments of HIV/AIDS pharmaceutical management systems Develop and implement HIV/AIDS pharmaceutical management training programs Implement innovative skills-building interventions for pharmaceutical management Contribute to country Global Fund proposals Contribute to country initiatives to improve adherence to ARV therapy Develop new pharmacy curricula that include pharmaceutical supply management
Ghana	WHO Collaborating Center for Advocacy and Training in Pharmacovigilance,[b] Centre for Tropical Clinical Pharmacology and Therapeutics, University of Ghana Medical School	Training in PV in African countries for building and strengthening of spontaneous ADR reporting systems Advocacy for PV across Africa either alone or in collaboration with WHO Promoting the integration of PV into PHPs Technical support to national PV centers Support communication and crisis management to national PV centers Acquisition (from WHO, UMC) and distribution of needed literature and technical tools to national PV centers and governments Research in PV including CEM of specified medicines Assistance in the development and maintenance of pregnancy registers Developed PV tools and guidelines (i.e., pharmacovigilance toolkit) with support from the Global Fund and WHO
Ghana	INDEPTH Effectiveness and Safety Studies of Antimalarials in Africa (INESS)[c]	Enable African researchers to carry out large phase 4 trials Provide objective country-specific effectiveness and safety data to inform global and national policy and practice Enhance African capacity to monitor local health systems to track the costs, effectiveness of coverage, and impact of newly registered antimalarial treatments
Morocco	WHO Collaborating Centre for Pharmacovigilance	Conduct and facilitate regional and national PV training courses for francophone, eastern Mediterranean, and Arabic countries Support WHO normative functions related to PV and promote patient safety Assist WHO in PV assessments and in the provision of technical support to member states in PV and patient safety
South Africa	WHO Collaborating Centre for Drug Policy was established in the Division of Clinical Pharmacology, Department of Medicine during December 1995, jointly with the School of Pharmacy at the University of the Western Cape	Monitor adverse reactions to medicines in South Africa, investigate national problems of drug toxicity, and recommend policy in this regard Provide medicines information to all levels of health professionals Provide a national medicines formulary for students, doctors, nurses, dentists, veterinarians, and community health workers to promote the WHO concept of essential medicines Monitor the way in which medicines are used nationally and internationally and develop policy based upon these trends, with special attention to the costs of medicines Develop a primary health care manual for traditional healers and develop database of traditional medicines Provide graduate programs in chemical and pharmaceutical analysis of herbal medicines and in screening activity Collaborate with international health agencies in the education and training of pharmaceutical support personnel in developing countries Develop programs in essential drug use at district hospitals and clinics

Country/ region	Name of institution/ organization/collaboration	Functions/terms of reference/training areas
Tanzania	St. Luke Foundation Kilimanjaro School of Pharmacy	Provides a professional Certificate Program in Drug Development, cGMP, and Quality Assurance
Tunisia	WHO Collaborating Centre for Drug Registration and Regulation	Strengthening the capacities of the Pharmacy and Medicines Unit to respond to the needs of the EMR and African countries in the field of management of regulation authorities and pharmaceutical control
		Offering study visit and training in the field of mechanism and organization quality assurance system in Tunisia
		Proceed to technical audit missions with regulation services and pharmaceutical control
		Training fellowship in the field of registry organization and management
		Development of follow-up system and evaluation of information registry system
		Elaboration of manual and guidelines for medicines registration
		Participate in national and international studies in rational medicines use and strengthening access to medicines
Tunisia	WHO Collaborating Centre for Quality Control of Medicines with a focus on training, research, and evaluation of marketing applications	Setting of standards and procedures in quality assurance system by giving opportunities to trainees in the anti-doping control laboratory which is World Anti-Doping Agency accredited
		Exchanges of scientific and technical information between other collaborating centers; this may be developed in analytical chemistry area
		Interlaboratory collaborative studies regarding the quality control of drug substances (proficiency testing scheme); like the WHO external quality assurance assessment
		Research training, rational research and development by providing opportunities to trainees in chemistry/anti-doping
		Analysis of samples on the request of WHO (quality control of drug substances and drug products)
		Organizing training courses with the collaboration of WHO in drug and vaccine evaluations
		Host trainees for the evaluation of pharmaceutical files and the analytical control of medicinal, biological, and vaccine products

[a]Matowe, L., Waako, P., Odoi Adome, R., et al. A Strategy to Improve Skills in Pharmaceutical Supply Management in East Africa: The Regional Technical Resource Collaboration for Pharmaceutical Management. *Human Resources for Health* 2008, 6:30 doi:10.1186/1478-4491-6-30. Available from http://www.human-resources-health.com/content/pdf/1478-4491-6-30.pdf

[b]http://www.pvafrica.org/index.php?option=com_content&view=frontpage&Itemid=69

[c]The four-year project to evaluate the safety and effectiveness of antimalarials is a collaborative project by African researchers in Tanzania, Ghana, Burkina Faso, and Mozambique. The INDEPTH project is supported by the University of Ghana, the Swiss Tropical Institute, Centers for Disease Control, the London School of Hygiene and Tropical Medicine, and the University of Cape Town. Available at http://www.indepth-network.org/iness/

Table 18. Institutions with PV Activities in Africa[a]

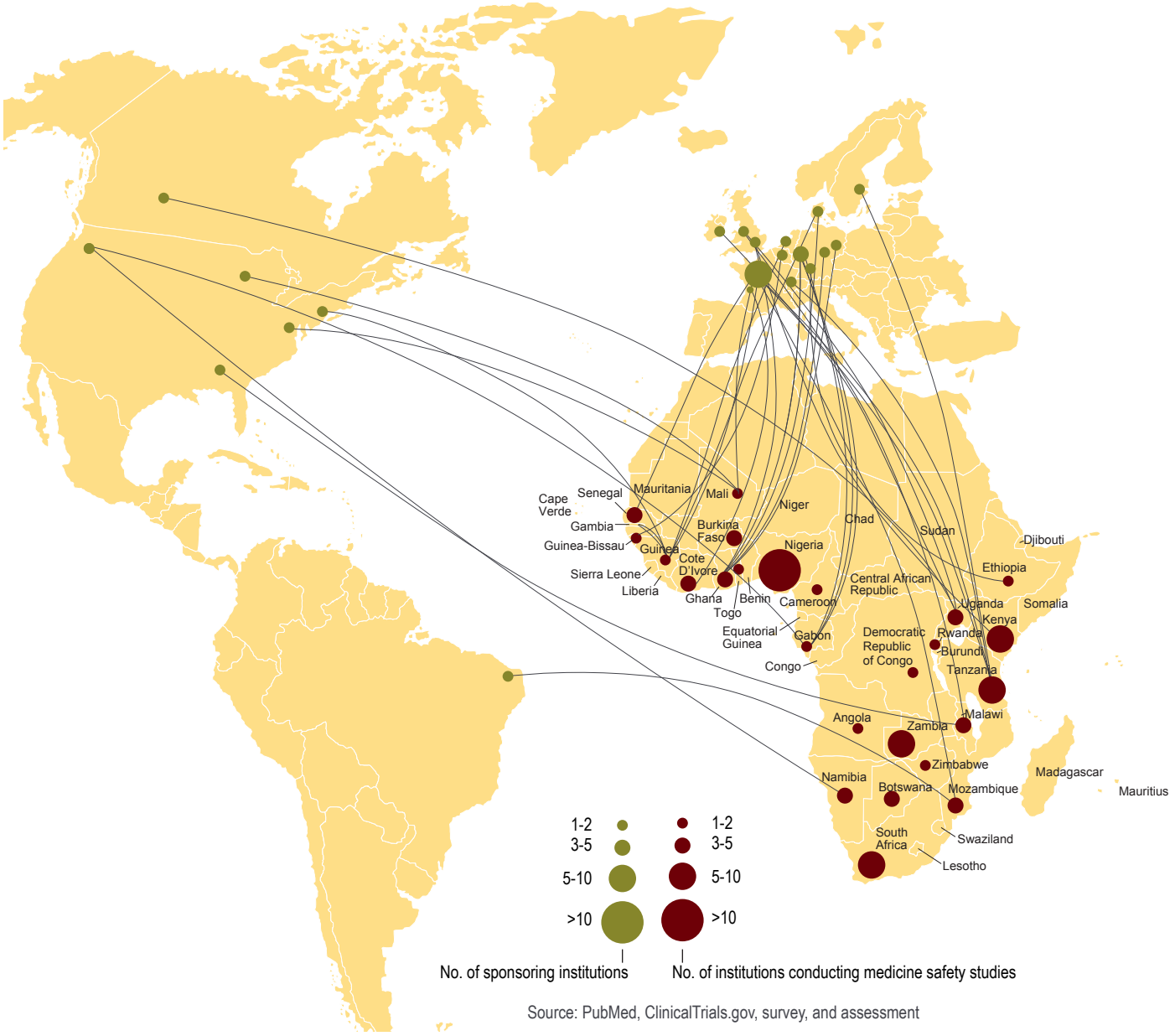
Country	In-country institutions with PV activities
Angola	PNCTL (TB control national program)
	Health provincial department (DPS)
Botswana	Botswana Harvard AIDS Institute
	Scottish Livingstone Hospital, Kweneng
	Princess Marina Hospital, Gaborone
	University of Botswana
Burkina Faso	Agence de Médecine Préventive
	Centre de Recherche en Santé de Nouna
	Centre de Documentation et d'Information sur le Médicament
	Institut de Recherche en Sciences de la Santé
Cameroon	Centre Mère et Enfant, Fondation Chantal Biya
	Faculty of Medicine and Biomedical Sciences, University of Yaounde
DRC	Programme National de Lutte contre la Trypanosomiase Humaine Africaine
	National Malaria Control Program (NMCP)
Côte d'Ivoire	Département de pharmacologie clinique, UFR SMA
	Université Cocody
	Programme PACCI
	Programme PACCI, Centre Hospitalo-Universitaire de Treichville
Ethiopia	Jimma University Hospital
Gabon	Albert Schweitzer Hospital, Lambaréné
Ghana	University of Ghana Medical School
	University for Development Studies, Tamale
	Kintampo Health Research Centre
	Dodowa Health Research Centre
Guinea	Centre Hospitalo Universitaire/Hôpital Ignace Deen, Conakry
Guinea-Bissau	Bandim Health Project
Kenya	University of Nairobi, KMTC
	Maseno University
	Wageningen University
	Kenya Medical Research Institute
	International Center for AIDS Care and Treatment Program (US program) in Kenya
	AIDS Relief in Kenya
Malawi	University of Malawi College of Medicine
	Malawi-Liverpool-Wellcome Trust Clinical Research Programme
	Malawi NMCP
	Research for Equity and Community Health Trust
Mali	Institut national de recherche en sante publique, BP, Bamako

[a]Disease programs, local academic institutions, teaching hospitals, and local nongovernmental organizations that conduct safety research and phase 4 studies and international institution sponsoring or collaborating with those local institutions for medicine safety research or PV activities (source: PubMed, ClinicalTrials.gov, survey, and assessment).

Country	In-country institutions with PV activities
Mozambique	Health Research Center of Manhica
	Manhica Health Research Centre
	Brazil's Agencia Nacional de Vigilancia Sanitaria
Namibia	Ministry of Health and Social Services
	Therapeutics Information and Pharmacovigilance Centre
	University of Namibia
Nigeria	National Institute for Pharmaceutical Research and Development
	Institute of Human Virology
	National Primary Health Care Development Agency
	Lagos State University College of Medicine
	University of Nigeria Teaching Hospital
	University College Hospital, Ibadan
	University of Port-Harcourt Teaching Hospital
	University College Hospital, Ibadan
	University of Benin Teaching Hospital
	Imo State University Teaching Hospital
	University of Ilorin Teaching Hospital
	University of Maiduguri Teaching Hospital
	NMCP
	National TB and Leprosy Control Program
	AIDS Prevention Initiative in Nigeria
Rwanda	TRAC Plus, Rwanda Biomedical Center
	National Institute for Pharmaceutical Research and Development
Senegal	L'Institut de Recherche pour le Développement
	Pharmacologie Université Cheikh Anta Diop
	Centre Antipoison Pharmacovigilance (medicine information center)
South Africa	Division of Clinical Pharmacology, University of Cape Town
	University of the Witwatersrand
	National Adverse Drug Event Monitoring Centre, Medicines Control Council
	University of Stellenbosch
	University of Durban-Westville
	South African Medical Research Council
	Africa Centre for Population Studies and Reproductive Health
	University of Natal
Tanzania	National Institute for Medical Research, Mwanza
	Ifakara Health Institute
	INDEPTH Effectiveness and Safety Studies of Antimalarials in Africa program
	Muhimbili University of Health and Allied Sciences (MUHAS)
	The Rufiji DSS
Togo	Programme Élargi de Vaccination (PEV)
	Les Programmes Nationaux de Lutte Contre la Tuberculose (PNLT)

Country	In-country institutions with PV activities
Uganda	Infectious Diseases Institute, Kampala
	Makerere University
	Mulago Hospital
	Gulu Regional Hospital
Zambia	Copperbelt University
	Tropical Diseases Research Centre
	Zambia Prevention, Care Treatment Program
	National Malaria Control Centre
	Center for Diseases Control in Zambia
Zimbabwe	University of Zimbabwe
	Medicines Control Authority of Zimbabwe

Figure 35. Collaboration on Medicines Safety Research and PV activities



Source: PubMed, ClinicalTrials.gov, survey, and assessment

Pharmacovigilance Systems in Selected Countries

Burkina Faso

The medicines in the public sector are mainly supplied by the Centrale d'Achat des Médicaments Essentiels Génériques, a central medical store in Burkina Faso and its regional warehouses. The private pharmaceutical sector is also thriving; in 2009, there were 8 private wholesalers, 166 licensed pharmacies, and 550 private drug stores. There is no local manufacturing capacity and the national medicines supply relies on imports.[160] The Direction Générale de la Pharmacie, du Médicament et des Laboratoires (DGPML) is the NMRA at the Ministry of Health responsible for drug registration, development, and enforcement of policy and regulations; regulation of pharmacies, wholesalers/distributors, and hospital pharmacies; control of medicines promotion and advertisement; coordination of the procurements in the public sector; quality assurance; control of clinical trials; and safety monitoring of medicines.[161] The Ministry of Health's NMRA established a PV unit (currently, Service des Vigilances) to coordinate activities related to medicines safety and quality at the national level and adopted an operational plan for the implementation of a national safety monitoring system in 2008. Two years later, it officially became a member of the WHO program.

The National Medicine Policy[160] recognizes

Pharmacovigilance Profile	
Policy, laws, and regulations	National Pharmaceutical Policy 2010 Arrêté N°2010-247/MS/CAB on creation of Direction Générale de la Pharmacie, du Médicament et des Laboratoires (DGPML) (draft regulation exists for PV)
Name of regulatory authority/website	DGPML; http://www.dgpml.sante.gov.bf/
Mandate of regulatory authority	Registration, licensing and import control, quality control, PV, control of promotion, control of clinical trials
How products get into the market	Registration by DGPML (list of registered products available at http://www.dgpml.sante.gov.bf/spip.php?page=liste_medic); importation only
Joined the WHO program	Official member, 2010
Landmark events	23.6 tons of counterfeits (worth USD 4.7 million) seized in 2008
E2B compliance	Through VigiFlow (E2B-compliant, web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports, reports from active surveillances, reports from pharmaceutical companies
Total # of ICSRs in the database	N/A (1986 in 2010)
Quantitative methods used in signal generation	The Bayesian Confidence Propagation Neural Network (BCPNN)
Newsletter or bulletin published	No

160 Ministere de la Sante. 2010. Politique Pharmaceutique Nationale. Ouagadougou: Burkina Faso.
161 Ministere de la Sante. 2010. Portant Organisation de la Direction generale de la pharmacie, du medicament et des laboratories. Ouagadougou: Burkina Faso.

the importance of monitoring adverse events, but there is no approved regulation to reinforce the policy. The institutional capacity for medicine safety monitoring is still weak in Burkina Faso; neither a safety advisory committee nor national PV guideline is in place yet, the staff members have no advanced trainings or skills to conduct all PV-related activities including processing ADR reports, infrastructure and tools are lacking, and roles and responsibilities of stakeholders are not clearly defined. The PV unit lacks the means of communication, such as newsletters or bulletins, to widely disseminate safety information to stakeholders and the public. There is a medicine information bulletin published quarterly by the Centre de Documentation et d'Information sur le Médicament, but there is no formal relationship between the PV unit and the center. The collaboration between the two bodies can leverage scarce resources and avoid duplication of efforts. The PV unit circulated several safety alerts and took regulatory actions in 2010, based on the information received from SRAs and WHO. However, a pragmatic procedure to monitor, assess, and communicate the information is still lacking.

PV is not well integrated into the health system of Burkina Faso. None of HIV/AIDS, TB, and malaria programs have structure, guidelines, or policy framework to implement PV activities. There is no systematic procedure in PHPs to collect and record the adverse event-related data. The assessment found that PV awareness among disease program managers is still very low and, consequently, the role and responsibilities of PHPs are not well understood. Similarly, the PV activities of documenting and reporting adverse events in hospitals and other health facilities were rarely observed.

The DGPML has made progress in establishing a PV system over the last three years. In particular, the implementation of active surveillance of vaccines helped the agency identify other priority medicines, such as ACTs and ARVs, for monitoring their risks and incorporating active approaches. Next steps will include developing the relevant legislation for medicine safety and quality monitoring, establishing a mechanism to coordinate PV activities among stakeholders, collaborating with PHPs to integrate PV into routine monitoring systems, strengthening the institutional capacity of the national PV center, sensitizing health care workers to increase awareness on monitoring and reporting adverse events, developing a national PV guideline or SOP to formalize the process, engaging research institutions and universities to conduct medicine safety research, and developing a comprehensive RMP.

Democratic Republic of Congo

The National Centre for Pharmacovigilance (CNPV), created by the Ministry of Health in June 2009, is affiliated with two faculties in the University of Kinshasa—the Faculty of Pharmaceutical Sciences and the Faculty of Medicine. DRC became an official member of the WHO program in September 2010. The Ministry of Health recognizes the need for and importance of a functioning national system for monitoring and taking measures to prevent adverse events. However, there is no legal provision to implement the PV activities at all levels of the health system. The CNPV has no dedicated budget from the government, but rather is supported by donors such as the Global Fund, WHO, and SPS.

The national safety advisory committee is composed of representatives from a wide range of stakeholders, such as departments of the Kinshasa University Teaching Hospital, Direction de la Pharmacie, Médicaments et Plantes médicinales (DPM), CNPV, professional associations, Ministry of Health, Ministry of Education, anti-poison center, quality control laboratory, and research institutions. However, the appointed committee is not yet functional. Currently, the PV technical committee comprised of experts from medicine, pharmacology, toxicology, and epidemiology is providing technical advice to the CNPV and the DPM for medicine safety related issues.

Pharmacovigilance Profile

Policy, laws, and regulations	National Pharmaceutical Policy 2005 Order 27a/Hygiene of March 15, 1933, on the practice of pharmacy and the Royal Decree of March 15, 1952, on the healing arts in the DRC (no regulation exists for PV)
Name of regulatory authority/PV center/ website	Direction de la Pharmacie, Médicaments et Plantes médicinales (DPM) National Centre for Pharmacovigilance (CNPV) No website
Mandate of regulatory authority	Registration, quality control, PV, control of promotion, licensing and import control, inspection, control of clinical trials
How products get into the market	No database of registered products exists[a]; local production and importation
Joined the WHO program	Official member, 2010
Significant events	N/A
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports
Total # of ICSRs in the database	1432 (156 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	Monthly newsletter

[a]An internal DPM ad hoc committee reviews the dossiers and makes the decision whether to accept the registration. No written documentation exists to guide this decision-making process.

Since 2009, several trainings were conducted to sensitize the health centers and hospitals by CNPV in collaboration with other partners. The reporting forms addressing ADR and treatment failure have been distributed to hospitals, yet the reporting rate is very low—2.4 per million in 2010. The capacity to process the data, evaluate the risks, and communicate the information is incipient. Safety alerts were not issued nor was action taken as a result of PV activities in 2010.

PV activities are not implemented in PHPs and health facilities in DRC. Collaboration between CNPV and PHPs has not been initiated; at most, a focal person in TB and immunization programs and some health care workers in the HIV program were trained on documenting and reporting adverse events. A survey of five DTCs showed that almost no (or minimal) activities related to medicine safety or PV have been conducted so far.

More efforts are required to help the newly established CNPV develop a functional PV system, establish the legal framework and national PV guidelines, assist the safety advisory committee to become functional, strengthen collaboration between CNPV and the DPM, incorporate product quality and medication error in the spontaneous reporting system, implement active surveillances to evaluate priority medicines in partnership with PHPs and academic institutions, establish a medicine information system for effective communication, use the safety information for decision making, and strengthen the roles of DTCs in ensuring medicine safety in health facilities.

Ghana

Ghana's Food and Drug Board (FDB) is the national regulatory body under the Ministry of Health, established by the Food and Drug Act, 1992. [162] The FDB is responsible for regulating the manufacture, importation, exportation, distribution, and the ethical standards in the use and advertisement of medicines, food, cosmetics, medical devices, and household chemicals. The Safety Monitoring Unit in the FDB is the national PV coordinating center. The University of Ghana Medical School initiated PV activity in 1992 at the Centre for Tropical Clinical Pharmacology and Therapeutics, which now provides technical support to the FDB. Ghana has developed basic structures for conducting PV activities, including a national PV unit with a mandate and structure, designated staff members, functional information and technology infrastructure, and collaboration with the WHO/UMC since 2001. However, across all levels (national, PHPs, and health facilities), the lack of a dedicated PV budget, a safety bulletin, PV training for health care workers, a mechanism to coordinate activities, and PV guidelines or SOPs was challenging the effective implementation of PV activities. The Ghana National Drug Policy[163] recognizes the need for PV and considers post-marketing surveillance as an important aspect of medicines registration and selection. It envisaged that a PV center should be responsible for identifying risk factors for and mechanisms underlying ADRs occurring in country. However, the Food and Drug Act 1992 does not address PV and has no section specifically requiring mandatory or voluntary reporting of adverse events.

Pharmacovigilance Profile	
Policy, laws, and regulations	The Ghana National Drug Policy 2004. Food and Drug Act 1992 (No regulation exists for PV)
Name of regulatory authority/website	Food and Drug Board http://www.fdbghana.gov.gh/
Mandate of regulatory authority	Registration, licensing and import control, PV, control of clinical trials, control of promotion, inspection, quality control
How products get into the market	Registration by FDB; registration by SRA, WHO prequalification, and the certificate of pharmaceutical product in WHO format referenced during registration (list of registered products available at http://www.fdbghana.gov.gh/); local production and importation
Joined the WHO program	Official member (2001)
Significant events	N/A
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports, PSURs, reports from PHPs
Total # of ICSRs in the database	1190 (107 in 2008, 171 in 2009, 467 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	No

The reporting forms are readily available at most levels of the health system. However, adverse events such as product quality, medication errors, and therapeutic ineffectiveness are rarely reported using the existing form. The current national PV guideline is targeted at the pharmaceutical industry and lacks critical elements that should be contained in a comprehensive guideline for all levels of the health care

162 PNDCL 3058, 1992. Food and Drugs Act, Available at http://www.epa.gov.gh/ghanalex/acts/Acts/FOOD%20AND%20DRUGS%20BOARD.pdf

163 Ministry of Health. 2004. Ghana National Drug Policy, 2nd ed. Accra: Government of Ghana. http://apps.who.int/medicinedocs/documents/s16185e/s16185e.pdf

system. These elements include defining roles and responsibilities of stakeholders, the scope of the PV and medicine safety system, methods for safety surveillance including both spontaneous reporting and active surveillance, and monitoring and evaluation.

The rate of ADR reporting is still low, although improvement has been made with spontaneous reporting (figure 36 and table 19). Challenges remain with poor data management and analysis of reports. PHPs in Ghana have a policy framework for PV and an organizational structure in place, which may enable the programs to be actively engaged in PV activities. The National AIDS Control Program and the NMCP are

Figure 36. Number of spontaneous reports in Ghana

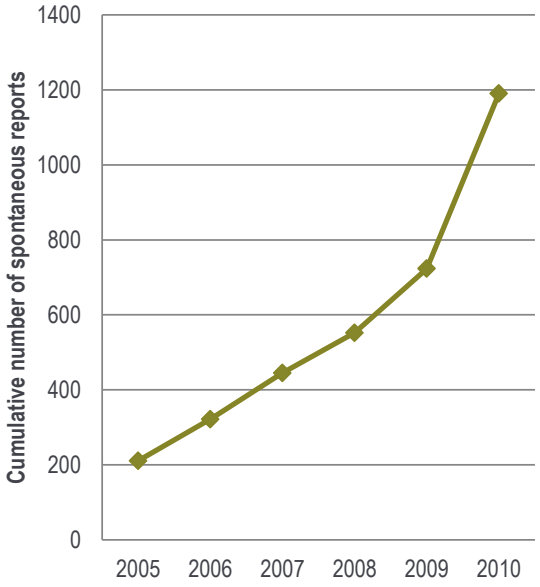


Table 19. Analysis of the Safety Monitoring Unit's 2009-2010 Annual Report

Type of report	Observed	Expected	Percent	Comments
Spontaneous report (×100)	4.7	23	20	Using 100 reports per million population
AEFI	15	22	68	Using 11.4 reports per 100,000 net doses distributed and assuming 200,000 doses distributed
Product quality reports (×10)	0.2	14.8	1	Using data from pharmaceutical counterfeiting: understanding the extent of a new transnational crime; average of China, India, Brazil for 2007[a]
International safety reports reviewed and acted on	2	38	5	Using the WHO pharmaceuticals newsletters 2010[61]
Safety communications (dear doctor/ health care professional letter)	4	38	10	Using the WHO pharmaceuticals newsletters 2010[61]

Note: Number of AEFI and product quality reports in 2009, other data in 2010.

Source: Interview with official in FDB and *Pharmacovigilance in Ghana: A systems analysis 2010*[74]

[a]Kuic, T. 2008. Pharmaceutical Counterfeiting: Understanding the Extent of a New Transnational Crime. The Police Chief LXXV:8. http://policechiefonline.org/magazine/index.cfm?fuseaction=display&article_id=1574&issue_id=82008

collecting data on patient responses to the medicines prescribed as well as ADRs and treatment failures. Efforts should be made to collate these routinely collected data and make them available to the PV center.

Several medicine safety projects and active surveillance studies have been conducted and are currently ongoing in Ghana—the majority related to malaria. The efforts to manage risks of using medicine by taking appropriate regulatory actions and disseminating safety information to a wide range of stakeholders, including the public, are still in the early stage. There is no communication channel, such as a safety newsletter or bulletin, to regularly disseminate safety alerts or the outcome of PV activities in Ghana.

The next steps to advance the PV systems in Ghana might include revising legislation to adequately address safety monitoring, developing a comprehensive national guideline, improving coordination of stakeholders, strengthening the DTC's role in health facilities, and implementing interventions to improve spontaneous reporting. These actions could be accomplished by enhancing the use of the existing reporting system to include other adverse events, using sentinel sites, collating adverse events from patient case files found in PHPs, developing a standard process to review and assess the priority medicine-safety issues through active approaches, and using the findings of PV activities to inform decision making.

Pharmacovigilance Profile	
Policy, laws, and regulations	The Kenya National Drug Policy 1994 and national pharmaceutical policy (draft) 2010; the Pharmacy and Poisons Act, Cap 244
Name of regulatory authority/website	PPB; http://www.pharmacyboardkenya.org/
Mandate of regulatory authority	Registration, licensing and import control, inspection, quality control[a], PV, control of promotion, control of clinical trials
How products get into the market	Registration by PPB (list of registered products available at http://www.pharmacyboardkenya.org/index.php?id=13); local production and importation
Joined the WHO program	Official member (2010)
Significant events	Thalidomide (birth defects, 1960), ARV counterfeits (approx. 15,000 batches found, 2011)
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports, product quality reports, active surveillance reports, PSURs
Total # of ICSR in the database	1490 (600 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	Biannual newsletter (available at http://www.pharmacyboardkenya.org/index.php?id=126)

[a]Conducted by the National Quality Control Laboratory for Drugs and Medical Devices, a semi-autonomous corporation.

Kenya

In September 2011, Kenya's NMRA, the Pharmacy and Poison Board (PPB), recalled more than 15,000 of batches of ARVs (generic version of Zidolam-N®), which were found to be a counterfeited version of WHO prequalified medicines and had been donated by a US charity to a local nongovernmental organization. The irregularities such as discoloration, molding, and breakages were reported by patients and health workers.[164,165] WHO issued a warning letter, and neighboring countries such as Tanzania and Uganda were alerted to investigate the circulation of counterfeits. These highly prevalent counterfeit medicines pose significant risks to public health in Kenya. To combat the problem of counterfeit and substandard medicines, PPB launched a PV program to monitor both the safety and quality of medicines in 2007 that instituted voluntary reporting, developed guidelines and reporting tools, and conducted a national sensitization workshop for health care workers. In June 2009, the Ministry of Medical Services committed to roll out the program nationwide, and the program obtained official membership in the WHO program in 2010.

The Pharmacy and Poisons Act, Cap 244, addresses the PPB's mission to ensure quality, safety, and efficacy of medicines. The PPB, with support from various stakeholders, has developed a standardized curriculum and a national guideline[166] to give an overview on the PV system structure and operations and guide health workers on how to monitor, detect, and report adverse events. Although the guideline spells out the pharmaceutical industry's roles and responsibilities to report ADRs to PPB and share post-marketing surveillance data, lack of policy and legislation to regulate the pharmaceutical industry makes it difficult to involve them in PV activities in Kenya. In fact, only one of four pharmaceutical companies surveyed had an SOP for PV and carried out post-marketing surveillance

164 PPB. 2007. Public Alert; Falsified Zidolam-N. Available at http://www.pharmacyboardkenya.org/index.php?id=155

165 European AIDS Treatment Group. 2011. Kenya: Fake HIV/AIDS Drug Confirmed on Sale. Available at http://www.eatg.org/eatg/Global-HIV-News/Access-to-treatment/Kenya-Fake-HIV-AIDS-drugs-confirmed-on-sale

166 Pharmacy and Poisons Board. 2009. Guidelines for the National Pharmacovigilance System in Kenya. 2nd ed. Available at http://www.pharmacyboardkenya.org/assets/files/national_pv_guidelines.pdf

activities. The Expert Safety Review Panel exists to provide technical advice on the safety of medicines and clinical trials, yet the function and technical capacity of the panel needs to be strengthened to fulfill its mandate.

The current reporting system incorporates the product quality by using a separate reporting form (pink form), but the system does not address medication error or treatment failure that should be also captured through a comprehensive reporting mechanism. The PPB also encourages all consumers to report any adverse events directly to the authority and advocated consumer reporting during the media conference in 2010. The consumer reporting is welcome progress for the national PV system, although its contribution to the reporting rate or the quality of consumer reporting has not been evaluated yet. In 2010, the PPB received 15 reports per million residents.

The PPB has worked with the Division of Malaria Control and the National AIDS and STI coordinating program to mobilize the scarce resources for PV, strengthen the surveillance system in existing disease control structures, and ensure the quality and safety of the expanded treatment. The PPB supported the set-up of five sentinel sites for antimalarials and seven for ARVs to boost reports of suspected ADRs and poor-quality medicines. The reports received from these sentinel sites accounted for the most reports received in 2009 and 2010; more than 60 percent received were ARV-related. The quality reports, along with product sampling and testing in these sentinel sites, resulted in the recall of already-circulating poor-quality medicines. The efforts should be expanded to collaborate with other programs, such as the national TB program and the immunization program, in sharing the PV data and using it for decision making.

Despite its short history of PV, Kenya has made rigorous efforts to address the medicine safety and quality issue. The PPB publishes biannual newsletters and also posts important safety alerts through an e-mail-based communication system called e-shot. A total of nine alerts were sent out in 2010 and consistent efforts are required to actively communicate the information with stakeholders through these channels. Various products have been recalled because of quality issues, and the PPB took regulatory actions including withdrawing products containing rosiglitazone and sibutramine and changing labels for cough and cold medicines containing mucolytics. However, the data management and evaluation of the risks is the system's main weakness. There is no real capacity to systematically scan and act on global safety alerts and evaluate the reports to generate and identify signals. There should be a standard process to analyze ADR reports received at the PPB, investigate further if necessary, and develop a comprehensive RMP for high-risk medicines. To improve Kenya's current PV systems functions and performance, all components of the PV system should be adequately addressed including strengthening policy and the legal framework, increasing capacity for risk evaluation, incorporating active approaches into the existing system, expanding the scope of PV to address all medicine-related adverse events, leveraging resources together with PHPs, and using the data to make regulatory decisions and revise relevant policy.

Pharmacovigilance Profile	
Policy, laws, and regulations	National Drug Policy 2003 National Agency for Food and Drug Administration and Control Act 1993 Good Pharmacovigilance practice regulations (draft) 2009 and Nigerian National PV Policy and implementation framework (draft) 2011
Name of regulatory authority/website	NAFDAC; www.nafdac.gov.ng
Mandate of regulatory authority	Registration, licensing and import control, inspection, quality control, PV, control of promotion, control of clinical trials
How products get into the market	Registration by NAFDAC; registration by SRA, WHO prequalification, and the certificate of pharmaceutical product in WHO format referenced during registration; online Automated Product Administration and Monitoring System, list of registered products available at http://registration.nafdac.gov.ng/; local production and importation
Joined the WHO program	Official member, 2004
Significant events	Chloroquine (14 deaths, 1989), DEG (109 deaths, 1990), DEG (approx. 80 deaths, 2008)
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	ADR reports, AEFI reports and reports from PHPs (limited data from active surveillances, pharmaceutical industry, and clinical trials are found in the database)
Total # of ICSRs in the database	8757 (310 in 2008, 2838 in 2009, 5140 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	Quarterly newsletter (available at http://www.nafdac.gov.ng/index.php?option=com_docman&Itemid=84)

Nigeria

The NAFDAC was established in 1993 to protect public health by promoting the quality, safety, and efficacy of processed food, medicines, cosmetics, medical devices, chemicals, and prepackaged water. There is pharmaceutical legislation in Nigeria including the Food and Drugs Act, Cap 150 of 1990; Counterfeit and Fake Drugs Act, Cap 73 of 1990; National Agency for Food and Drug Administration and Control Decree No. 15 of 1993; and the drugs and related products (registration) Decree No. 19 of 1993.[167] The NAFDAC is a part of Federal Ministry of Health and is a semi-autonomous agency with a number of functions—regulating and controlling the importation, exportation, manufacture, registration, inspection, advertisement, distribution, sale, and use of regulated products. As of 2010, NAFDAC had 1,500 staff members and receives the regular government budget for personnel, operational, and infrastructural costs, and external assistance to support its activities.[168]

Nigeria has experienced several tragedies as a result of adulterated medicines—14 children were reported dead after being administered chloroquine phosphate injections in 1989; 109 children died after taking paracetamol syrup produced with the toxic ethylene glycol solvent in 1990; and more than 80 children died after taking My Pikin Baby Teething Mixture in 2008.[18,169]

Since 1981, several attempts were made to establish a medicine monitoring program in Nigeria; these efforts gained only limited success because of the lack of consensus and awareness among stakeholders on the importance of monitoring ADRs, inadequate planning, limited expertise and skills, and lack of involvement of health care workers. In 2004, NAFDAC

167 Erhun W. O., O. O. Babalola, and M. O. Erhun. 2001. Drug Regulation and Control in Nigeria: The Challenge of Counterfeit Drugs. Journal of Health & Population in Developing Countries 4(2):23-34. Available at http://www.nigeriapharm.com/Library/Drug_regulation.pdf

168 Federal Ministry of Health and WHO. 2011. Nigeria Pharmaceutical Country Profile. Available at http://www.who.int/medicines/areas/coordination/nigeria_pharmaceutical_country_profile.pdf

169 Akunyili, D.N. 2005. Counterfeit Drugs and Pharmacovigilance, Presented at the 10th Pharmacovigilance-Study of Adverse Drug Reactions Training Course held at Uppsala Monitoring Centre, Sweden.

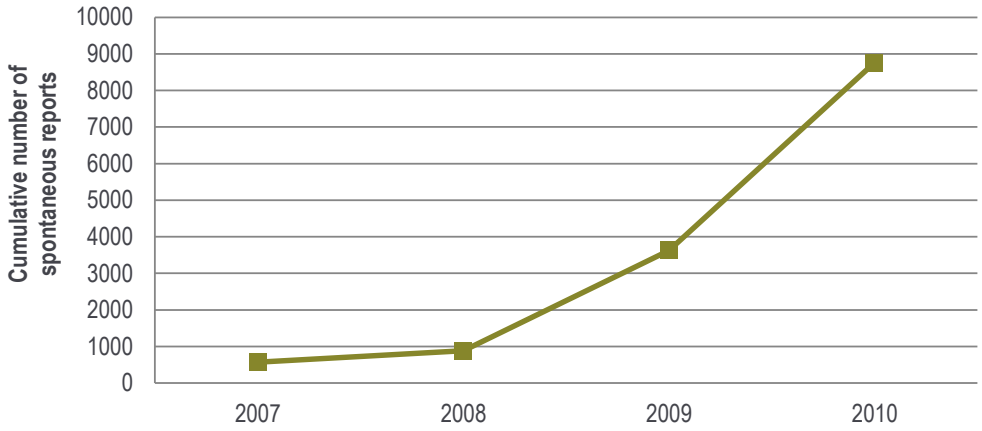
established a national PV program within the agency and became a member of the WHO Programme for International Drug Monitoring. The Federal Ministry of Health recognized the need to establish a functional program in Nigeria, which has the largest population in Africa and where a sizeable pharmaceutical market was emerging.

The NPC consists of a PV unit and the Food and Drug Information Centre (FDIC), responsible for promoting rational and safe use of medicines through monitoring medicine safety and providing information to the public. The NPC has a clear mandate; organizational structure; medicine information service; access to reference materials; PV guidelines for health workers,[170] pharmaceutical industry,[171] and monitoring antimalarials;[172] and functioning medicine safety advisory committee. Policies[173,174] and regulations[175,176] provide a sound framework to establish and strengthen a national PV system. The scope of PV involves all adverse events—product quality problems, ADRs, medication errors, and treatment failure related to medicines, herbal and traditional medicines, vaccines and biological products, medical devices, chemicals, and cosmetics.

The NPC has made efforts to sensitize the stakeholders at various levels of the health system and increase awareness on the need for detecting and reporting ADRs through spontaneous reporting; by organizing workshops/trainings for health care workers, health officers in zonal centers, consumers, and PHP staff; and distributing forms and guidelines. As a result, the number of ADR reports received and entered into the national database has gradually increased since 2004 and reached more than 5,000 (34 per million) in 2010, yet is still under the target of 100 per million (figure 37).

The NPC complements its spontaneous reporting program by incorporating active surveillance into the national PV system to detect and evaluate the risks associated with ACTs (box 9) in close collaboration with NMCP. Furthermore, the NPC became

Figure 37. Spontaneous reporting in Nigeria



170 NAFDAC. 2008. A national pharmacovigilance guideline, 2nd ed.
171 NAFDAC. Guide for Reporting Adverse Reactions to Marketed Drugs: Guide for Pharmaceutical Industry in Nigeria.
172 NAFDAC. 2010. Field Guide for Cohort Event Monitoring (CEM) of Antimalarials in Nigeria.
173 Federal Ministry of Health. 2005. National Drug Policy, 2005.
174 NAFDAC. 2011. Nigerian National Pharmacovigilance Policy and Implementation framework (final draft)
175 NAFDAC. 1993. National Agency for Food and Drug Administration and Control Decree No. 15
176 NAFDAC. 2009. Good Pharmacovigilance Practice Regulations (draft), 2009.

a subrecipient of the Global Fund-AMFm grant through NMCP that shall provide an additional financial support for expanding capacity. Efforts have been made to establish a close collaboration with other PHPs. The NPC provided a training manual for health care workers in the Global HIV/AIDS Initiative Nigeria program and coordinates the on-going epidemiological study of ARVs. The National Tuberculosis and Leprosy Control Program was supported to adapt the reporting form as part of a reporting tool in the national treatment guideline for TB.[177] The National Primary Health Care Development Agency was also encouraged to share the information on AEFI with the NPC. In spite of all these efforts and policy framework in disease programs.[8,178,179,180] PV is not fully implemented in the PHPs yet. The assessment found that the system or structure to collate and aggregate safety data in the central level of PHPs is not in place and, consequently, information sharing with the NPC is weak.

Nigeria has taken important regulatory actions as a result of reviewing the PV data obtained from local and external sources: this has led to labeling changes, withdrawal of licenses, product recall, reclassification, and enforcing risk management practices. To communicate the safety information and these decisions, the NPC issues quarterly newsletters, safety alerts, and public announcements on the NAFDAC website (www.nafdac.gov.ng).

The PV system in Nigeria has significantly improved over past years. To sustain the functioning and effective PV system, greater efforts are required in coordinating various stakeholders including development partners, pharmaceutical industry, academic institutions, DTCs in health facilities, and professional bodies and enhancing the integration of PV in PHPs in Nigeria.

Box 9. Cohort Event Monitoring of ACTs in Nigeria

There was a clear need for an active approach to evaluate the safety of ACTs due to the wide availability of ACTs as an over-the-counter drug and little data regarding adverse events in the Nigerian population. The NPC, in collaboration with NMCP, Society for Family Health, Yakubu Gowon Centre, and WHO, started a pilot cohort event monitoring in 2008. The pilot took place at 6 sites across regions; it targeted 3,000 patients and was scaled up to include 10,000 patients in 2010. Key findings from the pilot study include—

- The common adverse events were general body weakness (40 percent), dizziness (13 percent), abdominal pain (6 percent), sleeplessness/insomnia (5 percent); the worst symptoms occurred on the third day of the treatment.
- There was causal relationship between the observed adverse events and use of ACTs in the cohort.
- The common identifiable risk factors were concomitant use of herbal medicines, use of ACTs during pregnancy, and age under 20.
- Although there was no significant difference in treatment outcome between artemether-lumefantrine and artesunate-amodiaquine, artemether-lumefantrine seemed to have a better safety profile than artesunate-amodiaquine.
- There were two cases of life-threatening events and two cases requiring prolonged hospitalization associated with artesunate-amodiaquine.
- Appropriate use of ACTs was still an issue including inadequate prescribing and incorrect use among the public.

The final outcome of the study will provide the agency and other countries in Africa with useful information for implementing evidence-based intervention to ensure safe and appropriate use of ACTs.

Source: Interview with a staff member from NPC, NAFDAC

177 National TB and Leprosy Control Programme. Workers Manual. 5th ed.
178 Federal Ministry of Health. 2010. National Policy on Malaria Diagnosis and Treatment.
179 National Primary Health Care Development Agency. 2009. National Immunization Policy.
180 Global HIV/AIDS Initiative Nigeria. 2005. Technical Strategies. http://www.fhi360.org/NR/rdonlyres/ejo6cnei63tdlvxwgky7auvml4jslzkc4ivmxudzvlhwsltwxffofruknca5n4vmmqqjlppvfgh74j/GHAINStrategiesenhv1.pdf

Senegal

Pharmacovigilance Profile	
Policy, laws, and regulations	National Pharmaceutical Policy 2006 Décret N° 2004-1404 on the creation of DPL Arrete portant organization du system National de Pharmacovigilance 2009
Name of regulatory authority/PV center/ website	Direction de la Pharmacie et des Laboratoires (DPL) Le Center Antipoison No website
Mandate of regulatory authority	Registration, import control, inspection, quality control, PV, control of promotion, control of clinical trials, (licensing by professional council)
How products get into the market	Registration by DPL (No. of registered drugs: 2915); local production and importation
Joined the WHO program	Official member (2009)
Significant events	N/A
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports, PSURs, active surveillance reports, reports from PHPs, reports from clinical trials
Total # of ICSRs in the database	265 (120 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	Quarterly newsletter

Direction de la Pharmacie et des Laboratoires (DPL) was established in 2004 under the Ministry of Health and Disease Prevention by legislation No. 2004. The legislation provides for the regulation of medicines, raw materials, medical devices, and cosmetics as well as clinical trials of regulated products. Its mission is to assess the benefits and risks associated with the use of health products and ensure the implementation of various measures to minimize the risks and evaluate and control the use of regulated products. The first attempt to establish a medicine monitoring program was started in 1998 by the Ministry of Health, although the program became active in 2009 with a reinforced policy[181] to implement a national PV system under the responsibility of DPL. DPL is monitoring and coordinating all activities related to medicine safety issues at the national level. It closely collaborates with Le Center Antipoison and its technical committee, which is responsible for conducting causality assessments of reports collated and forwarded by DPL, assessing the risks of medicines by implementing epidemiological studies, if necessary, and transmitting the outcome of assessment to DPL for further actions or appropriate decisions. The technical committee also supports the National Commission of Pharmacovigilance whose mission is to recommend decisions to the Minister of Health to prevent possible harms identified by PV activities, to propose a research or active surveillance for further investigation, and to promote PV among the wide range of stakeholders (figure 38). The roles and responsibilities of the committees were discussed and defined during their first meetings in 2010 and, therefore, it is important to sustain the efforts and strengthen the technical capacity of the committees.

A national PV guideline developed[182] in consultation with various stakeholders provides standards and directions on definitions; both passive and active approaches; scope of PV including medication errors, product quality, and treatment inefficacy; roles

181 Ministere de la Sante et de la Prevention. 2009. Arrete portant organization du system National de Pharmacovigilance.

182 Direction de la Pharmacie et des Laboratories. 2010. Guide National de Pharmacovigilance. Dakar: Government of Senegal.

and responsibilities of stakeholders; and processes for coordinating the activities in Senegal. The guideline recommends that the reporting form be filled out by health care professionals for any adverse events and that any serious or unexpected event is reported to the DPL within 24 hours. It also provides guidance for pharmaceutical industries to report any adverse event (including AEFI), submit a PSUR, and prepare

Figure 38. Structure of PV system in Senegal

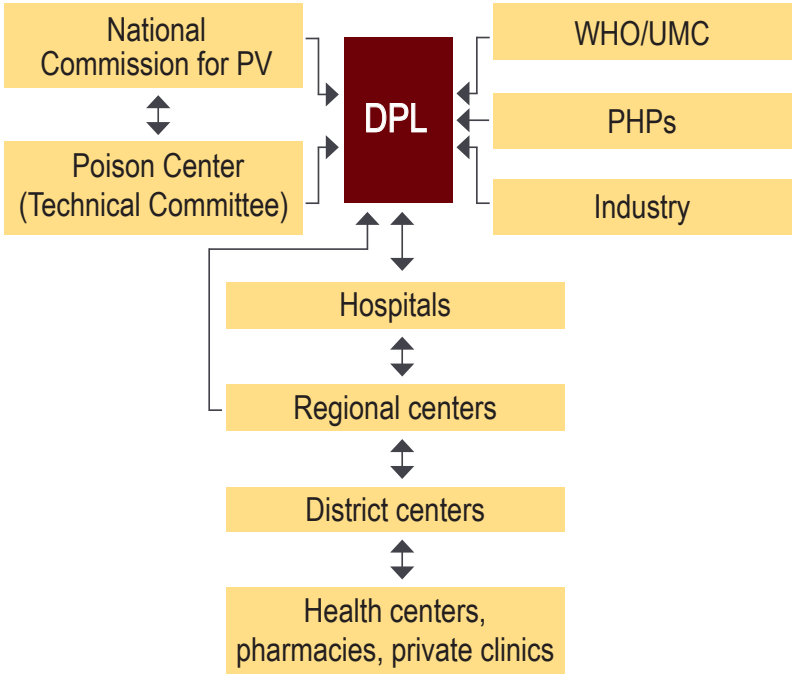
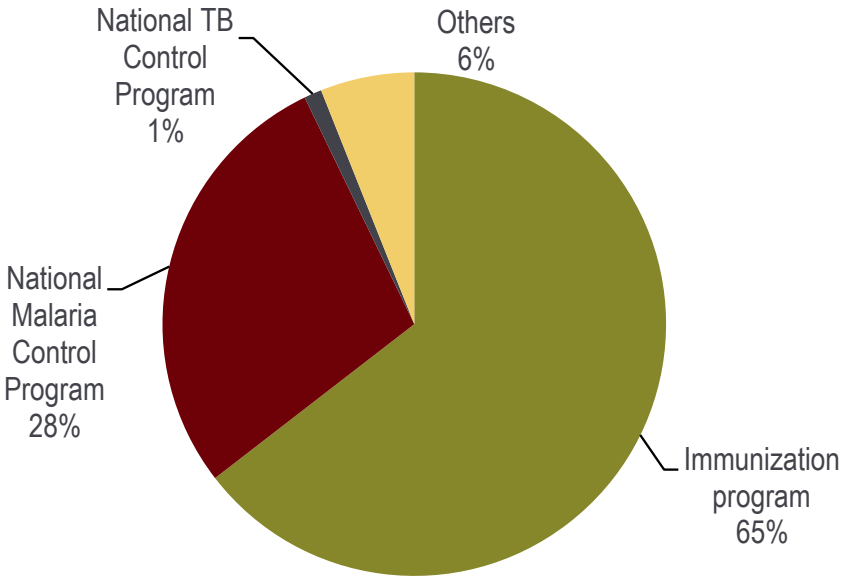


Figure 39. Sources of adverse event reports in Senegal



Note: Analysis of reports received from August 2009 to October 2010
Source: Report for technical committee meeting in December 2010

an RMP when requested by the DPL, which is enforced by the regulation[183]. However, compliance of the pharmaceutical industry to the regulation remains unknown.

The reporting rate in Senegal is still very low (10 per million in 2009 and 2010), and most reports were received from immunization and malaria programs (figure 39). In fact, the immunization program, participating in the Global Network for Post-Surveillance of Newly Prequalified Vaccines program, collaborates with the DPL in strengthening the surveillance system to monitor and report AEFI and sharing the safety data. Health facilities including hospitals, regional medical centers, and health centers are not active in monitoring and reporting adverse events. None of six health facilities surveyed sent any report to DPL in 2010, which also corresponds to poor-functioning DTCs to ensure safety, quality and rational use of medicines at the health facility level.

The capacity for risk evaluation and communication is still weak in Senegal. The DPL decided to withdraw several products (i.e., rosiglitazone, bufexamac) from the market following the regulatory decisions made by SRAs in 2010, although a systematic procedure to assess the safety alerts from external sources and locally collected data is lacking. The DPL started to publish its bulletin in 2011, including medicine information, medicine policy update, and activities of the authority. Consistent efforts are required for effective communication of important safety issues to the public and all stakeholders by various channels— bulletins, dear doctor letters, MoH circulars, press releases, etc.

Overall, the organizational structure, legal framework for PV, and collaboration with in-country and international stakeholders exists to support PV activities in Senegal, but functions of the national PV system to collect, analyze, and use medicine safety and quality information need to be strengthened. This can be accomplished by involving health facilities in PV activities; incorporating active approaches to ensure medicine safety and quality, such as epidemiological studies, product quality surveys, or medicine use studies; strengthening the technical capacity of national PV committees; establishing a formal process to regularly monitor and assess the external safety alerts; collaborating with all PHPs, including TB and HIV/AIDS programs; and strengthening the information flow between the poison center and DPL.

183 Direction de la Pharmacie et des Laboratories. 2008. Note d'information destinee aux enterprises pharmaceutiques sur les exigencies reglementaires en pharmacovigilance au Senegal. Dakar: Government of Senegal.

South Africa—PV in the Pharmaceutical Industry

Pharmacovigilance Profile	
Policy, laws, and regulations	National Drug Policy for South Africa 1996 Medicines and Related Substances Control Act 1965 The Medicines and Related Substances Control Act, Act 90, Regulations 34 and 37, 1997
Name of regulatory authority/PV center/ website	The Medicines Control Council http://www.mccza.com/ National Adverse Drug Event Monitoring Center (NADEMC)
Mandate of regulatory authority	Registration, licensing and import control, inspection, PV, control of promotion, control of clinical trials
How products get into the market	Registration by MCC; South Africa is a member of PIC/S (number of registered drugs as of 2009: 12,083); local production and importation
Joined the WHO program	Official member (1992)
Significant events	6 maternal deaths from Stevens Johnson Syndrome and liver failure associated with use of nevirapine in 2011
E2B compliance	N/A
Medical terminology used	N/A
Type of reports in PV database	N/A
Total # of ICSRs in the database	N/A
Quantitative methods used in signal generation	N/A
Newsletter or bulletin published	No

The Medicines Control Council (MCC), under the Medicines and Related Substances Control Act,[184] oversees South Africa's regulation of medicines, including PV, and ensures ethical standards in advertisement and promotion of medicines. The MCC established a National Adverse Drug Event Monitoring Center (NADEMC) in collaboration with the University of Cape Town in 1987 to monitor the safety of medicines by voluntary reporting of suspected adverse events by industry and health professionals. The regulations[185] and the national guideline[186] require the MAH to report all adverse events, ensure safe use, and collect real-life safety and effectiveness data on the product.

A web search identified between 60 and 100 pharmaceutical companies in South Africa. The total pharmaceutical market size estimated from the sales figures of leading corporations was about USD 2.7 billion in 2009, and generics accounted for 21 percent of the total market.[187] Local production capacity is limited to final formulations and last-step synthesis with the exception of one company producing active pharmaceutical ingredients.[188]

An assessment of the pharmaceutical industry PV in South Africa was conducted from September 2010 to September 2011, including ten MICs, five MGCs, five LOCs, and five clinical research organizations (CROs). The assessment of the pharmaceutical industry found that most companies surveyed, except LOCs, have internal policies that contain essential statements on PV or medicine safety monitoring. SOPs were in place for expedited reporting of serious ADRs and submitting PSURs, which comply with the national regulatory requirements. However, the reference to the most updated, specific regulations and guidelines was often missing in the documents,

184 The Medicines and Related Substances Control Act, Act 101, 1965.
185 The Medicines and Related Substances Control Act, Act 90, Regulations 34 and 37, 1997.
186 Medicines Control Council. 2011. Reporting adverse drug reaction in South Africa (ver 2).
187 IMS Health. 2010. IMS Market Prognosis South Africa 2010-2014.
188 Bumpas, J. and E. Betsch. 2009. Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines.Washington, DC: World Bank. Available at http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/APIExploratoryStudy.pdf

and respondents in industry demonstrated poor understanding of the national regulatory framework.

The basic structures for conducting PV activities were in place, including PV units with a clear mandate and roles and responsibilities, designated persons for PV, information technology infrastructure, and reporting lines within the company. Although all companies had one or several staff responsible for ensuring product safety, the existence of a dedicated unit for PV varied across the companies; all MICs, 4 of 5 MGCs, 2 of 5 LOCs, and none of the CROs have a PV unit. A dedicated PV budget, PV training for staffs, an information sharing process, and coordination of all stakeholders including other teams in the company, such as marketing or sales team, were lacking across all companies.

The companies are routinely reporting ADRs to the national regulatory authority (table 20), but monitoring and reporting other adverse events, such as product quality and lack of efficacy, was not a part of the routine process (table 21). Although multinational companies have a safety database collating all country data at the central level, data collation of medicine safety and PV data at the local level was poor; 30 percent of the respondents from MICs, 40 percent of the respondents from LOCs, and no MGCs and CROs acknowledged that a safety database is available at the local level. A medical information service exists in more than 80 percent of the companies surveyed, but the evaluation and compilation of medical information queries and product quality complaints was poorly coordinated in most cases. Most of the companies surveyed had neither a standardized process to scan safety data from locally relevant publications (i.e., there are more than 50 African journals including 32 South African journals relevant to medicine safety) nor frequent reviews of those resources.

The pharmaceutical industry's efforts in South Africa to identify safety signals and evaluate the risks are still insufficient. Most of companies surveyed did not specify or implement a process to identify safety signals from change in severity, characteristics, or frequency of expected ADRs or unexpected SAE. For instance, the systematic review of reported safety data was rarely performed and none of surveyed companies had statistical or mathematical tools (i.e., data mining software such as WHO's

Table 20. Number of ADR Reports Processed and Reported in the Last Year

	MICs	MGCs	LOCs	CROs
No. of products in market[a]	3-55 (median 35)	8-137 (median 13)	4-200 (median 30)	N/A
No. of reports sent to MCC in the last year	5-978 (median 286)	0-1[b]	0-240 (median 59)	2[c]

[a]This might include a number of different formulations with the same active ingredient.

[b]3 of 5 companies did not have the data available for review

[c]4 of 5 companies did not have the data available for review

Table 21. Monitoring Product Quality and Lack of Efficacy

	MICs (%)	MGCs (%)	LOCs (%)	CROs (%)
SOP to monitor product quality exists	70	0	20	0
SOP to monitor treatment failure exists	70	20	20	N/A

Vigibase) at the local level. The assessment found that active surveillance activities including phase 4 studies and submission of PSURs were lacking across all companies surveyed (table 22). In particular, respondents from multinational companies indicated that they don't usually get involved in aggregating local data for PSUR, but instead merely submit the PSUR received from headquarters to the local regulatory authority.

Risk management and communication activities were rarely in place or implemented (table 23). Even if RMPs for high-risk medicines are available at industry headquarters, implementation of such plans in South Africa was rarely observed. Similarly, only two of five local companies confirmed that they have implemented some types of risk mitigation activities.

Overall, a scope of operational activities for PV units or designees in pharmaceutical companies in South Africa was often limited to collection of adverse events and submission of reports to the national regulatory authority. Data collation, risk evaluation, and decision making are usually carried out by multinational company headquarters or barely incorporated into the routine PV activities of local companies. However, South Africa shows some encouraging trends of PV development in the pharmaceutical industry. Interestingly, multinational companies require local affiliates in South Africa to coordinate PV activities within the companies located in other African countries. Hence, South African industry can play a significant role to enhance a regional capacity for PV in industry of SSA.

The following aspects should be considered to strengthen the current PV system in South Africa pharmaceutical industry—improving the policy, SOPs, and internal process to meet the local requirements and regulations; strengthening the technical capacity of the local PV unit or designee to carry out all aspects of PV activities; developing a formal information sharing and tracking process among different units in the company and among consumers and other stakeholders; developing a process to collate, review, and evaluate local safety data, publications, and medicine information queries; enhancing the scope of PV including all other adverse events; and developing a strategy or process to ensure compliance to PV requirements internally (i.e., self-audit).

Table 22. Number of PSURs Submitted in the Last Two Years

Number of PSURs submitted in the last 2 years	MIC	MGC	LOC
Upon MCC request	2	3	4
As a part of registration package	22	0	1
On a voluntary basis	34	1	1

Note: The current guideline requires the MAHs to submit all nonserious ADR reports occurring in South Africa with any medicine on an annual basis as a summary report. If necessary, a summary report can be requested by the MCC for any other time period.

Table 23. Safety Actions Taken in the Last Two Years

Safety actions taken	MICs	MGCs	LOCs	CROs
Number of RMPs submitted to MCC in the last 2 years	1	0	2	0
Interventional measures on market in the last 5 years (i.e., label change, package insert update, boxed warning)	32	1	3	0
Interventional measures on product in the last 5 years (product recall, withdrawal of license)	2	2	3	1

Tanzania

Tanzania Food and Drugs Authority (TFDA), a semi-autonomous body under the Ministry of Health and Social Welfare, is a regulatory authority responsible for controlling the quality, safety, and effectiveness of food, drugs, herbal drugs, cosmetics, and medical devices. It is established under Tanzania Food, Drugs and Cosmetics Act No. 1 of 2003, amendment to Pharmaceutical and Poisons Act No. 9 of 1978, and Food Act No. 10 of 1978.[189]

Pharmacovigilance Profile	
Policy, laws, and regulations	Tanzania Food, Drugs and Cosmetics Act 2003 National Medicines Policy 1991
Name of regulatory authority/website	Tanzania Food and Drugs Authority (TFDA; http://www.tfda.or.tz/)
Mandate of regulatory authority	Registration, licensing and import control, inspection, quality control, PV, control of promotion, control of clinical trials
How products get into the market	Registration by TFDA (list of registered products available at http://www.tfda.or.tz/registered_products.php); local production and importation
Joined the WHO program	Official member (1993)
Significant events	A number of Stevens Johnson Syndrome cases associated with the use of sulphadoxine/pyrimethamine reported by media in 2002
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, AEFI reports
Total # of ICSRs in the database	N/A (126 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	No

The PV program was first introduced in 1989 by the Tanzania Drug and Toxicology Information Service, a drug information center in the Muhimbili National Hospital. The information service was to provide medicine information and education for the public and health care workers, collect and analyze ADR reports, and promote rational use of medicines.[190] Tanzania implemented a spontaneous reporting scheme in 1993 and became the second official member of the WHO program in Africa following South Africa. In 1998, the information service was incorporated into the Ministry of Health and Social Welfare and the national PV program became one of the core functions of TFDA with its establishment in 2003. The TFDA has since decentralized the PV system by setting up four zonal PV centers in referral hospitals and regional PV centers in regional hospitals.

The Tanzania Food, Drugs and Cosmetics Act provides a regulation for PV such that "the TFDA shall ensure that evidence of existing and new adverse events, interactions and information about PV of products being monitored globally, are analyzed and acted upon."[194] However, it doesn't provide a legal mandate for the pharmaceutical industry, which makes it difficult to engage pharmaceutical companies in reporting adverse events to the regulatory authority and conducting post-marketing surveillance activities. The TFDA developed a national PV guideline[191] and a technical committee. The committee, composed of experts from PV, clinical pharmacy, clinical

189 The Tanzania Food, Drugs and Cosmetics Act, 2003. Available at http://www.tfda.or.tz/downloads/guides/tfda_fees_regulations.pdf

190 Tran, D., E. Rutta, P. Risha, and A. Burke. 2006. A Consultative Meeting Report for Pharmacovigilance: Tanzania and Beyond. Submitted to the US Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

191 Tanzania Food and Drugs Authority. 2010. National Guideline for Monitoring Medicines Safety, 2nd ed. Document no. TFDA/DMC/PV/001

pharmacology, public health, medicines, pharmacy, and dentistry, held its first meeting in 2010 to define its roles and responsibilities, review the national guideline, and review the active surveillance implementation manual.

The TFDA developed separate forms to report ADRs and product quality, which can also be filled out online through the TFDA website. The current form doesn't address medication error or treatment failure, although the TFDA recognizes the need to cover all adverse events and the updated guideline requires those problems to be reported through the existing reporting scheme. The TFDA also encourages patients to report adverse events by using the simplified patient reporting form. All reports are entered into the Vigiflow database by TFDA and its zonal and regional PV centers.

TFDA introduced CEM of artemether/lumefantrine in four regions targeting 10,500 cohorts in 2009; the monitoring is ongoing. TFDA developed data collection tools, a CEM implementation manual, and brochures for patients and conducted training and workshops for health care workers. The questionnaires filled by health care workers are sent to the TFDA and entered into CEM database. About 4,000 patients' data have been collected through October 2010, but no interim analysis has been conducted yet.[192] TFDA identified the availability of artemether-lumefantrine, Internet connectivity for data entry, and budget constraints as main challenges for implementing active surveillance. Also, there is ongoing CEM of dihydroartemisinin and sentinel sites established to monitor ARVs in collaboration with UMC with the support of the BMGF.

Despite its well-organized structure and the relatively long history of the PV program, the reporting rate is very low (3 per million in 2010, the lowest reporting rate among groups 3 and 4) and the capacity to process and evaluate the data including causality assessment is weak. The assessment found that there was no safety issue or signal generated locally in 2010 and only 8 percent of locally relevant safety alerts from SRAs were acted on. Also, information sharing with stakeholders including PHPs (i.e., no AEFIs reported to the TFDA) was poor and communication channels such as safety bulletins or newsletters were not in place. The national PV system in Tanzania can be further enhanced by establishing a standard process to evaluate and use the local and global safety data, developing an effective communication strategy, sharing information with PHPs including immunization programs, and making continuous efforts to engage zonal and regional PV centers in collecting the reports from all levels of health system.

192 Pharmacovigilance Technical Committee Meeting minutes, Oct 2010.

Uganda

Pharmacovigilance Profile	
Policy, laws, and regulations	National Drug Policy and Authority Act Cap 206, 1999 Uganda National Drug Policy, 2002 (No regulation exists for PV)
Name of regulatory authority/website	National Drug Authority http://www.nda.or.ug/
Mandate of regulatory authority	Registration, licensing and import control, inspection, quality control, PV, control of promotion, control of clinical trials
How products get into the market	Registration by NDA; registration by SRA, WHO prequalification, and the certificate of pharmaceutical product (CPP) in WHO format referenced during registration (list of registered products available at http://www.nda.or.ug/register.php); local production and importation
Joined the WHO program	Official member (2007)
Significant events	Quinine inj. (45 children crippled, 2009)
E2B compliance	Through VigiFlow (E2B-compliant web- based portal)
Medical terminology used	WHO-ART
Type of reports in PV database	Spontaneous reports, PSURs, reports from clinical trials
Total # of ICSRs in the database	735 (75 in 2008, 222 in 2009, 180 in 2010)
Quantitative methods used in signal generation	BCPNN
Newsletter or bulletin published	Biannual newsletter

The National Drug Authority (NDA) was established in 1994 under Section 3(1) of the National Drug Policy and Authority Act Cap 206.[193] It implements the mandate of the NDA through the functions of medicines assessment and registration, inspectorate services, quality control, and medicine information/PV. Situated in the Drug Information Department of NDA, the Uganda NPC was established in 2005 and became a member of the WHO Programme for International Drug Monitoring in 2007. A national drug policy[194] contains a basic framework for PV, but there is no legislation or regulation to provide a legal mandate. The NPC is well equipped with manuals and SOPs for handling spontaneous reports, providing acknowledgment to reporters, conducting causality assessment for each case report, and providing feedback to the reporter on the assessment outcome. Assessing and investigating safety and quality issues are carried out in close collaboration with other units such as the drug inspectorate, quality control lab, and a registration unit that brings collective and effective actions together. The national PV and clinical trial committee provides guidance to the NPC by overseeing the policy and legal instruments, promoting PV at various levels, and giving advice on PV-related issues. A national PV guideline[195] that incorporates a comprehensive scope of PV has been developed and distributed to the hospitals and health centers.

Uganda's PV system has been decentralized through establishing PV centers in regional referral hospitals (figure 40). Currently, there are 14 regional centers established throughout the country, which are managed by a regional coordinator. Regional centers' activities include increasing awareness of monitoring adverse events among district health workers and hospital staff, distributing reporting forms, and collecting the forms. Most coordinators enter the collected information directly into Vigiflow and transmit it to the NPC for further processing and analysis. The decentralized system helped to collate the reports without a physical delivery to the capital, Kampala,

193 Ministry of Health. 1999. National Drug Policy and Authority Act.
194 Ministry of Health. 2002. Uganda National Drug Policy. http://apps.who.int/medicinedocs/documents/s16463e/s16463e.pdf
195 National Drug Authority. 2009. A Guide to Detecting and Reporting Adverse Drug Reaction.

and provide feedback to reporters in a timely manner by a regional coordinator. In addition to regional centers, the national PV center works closely with seven regional NDA offices and district health offices to distribute the forms and collect the reports. However, not all regional centers are actively engaged in collecting and reporting medicine-related adverse events to the NPC. Consistent training and supervision are required to sensitize and encourage the regional centers to increase the reporting rate (figure 41). Further, the responsibility of DTCs in those hospitals to review and use the information should be strengthened by linking them with the regional PV centers.

The NPC has made an effort to incorporate active approaches and formal research methods in the system to evaluate potential problems and provide measures of the level of potential risks (table 24). Those efforts include establishing a memorandum of understanding with Makerere University to study the combination of sodium

Figure 40. Organizational structure for PV in Uganda

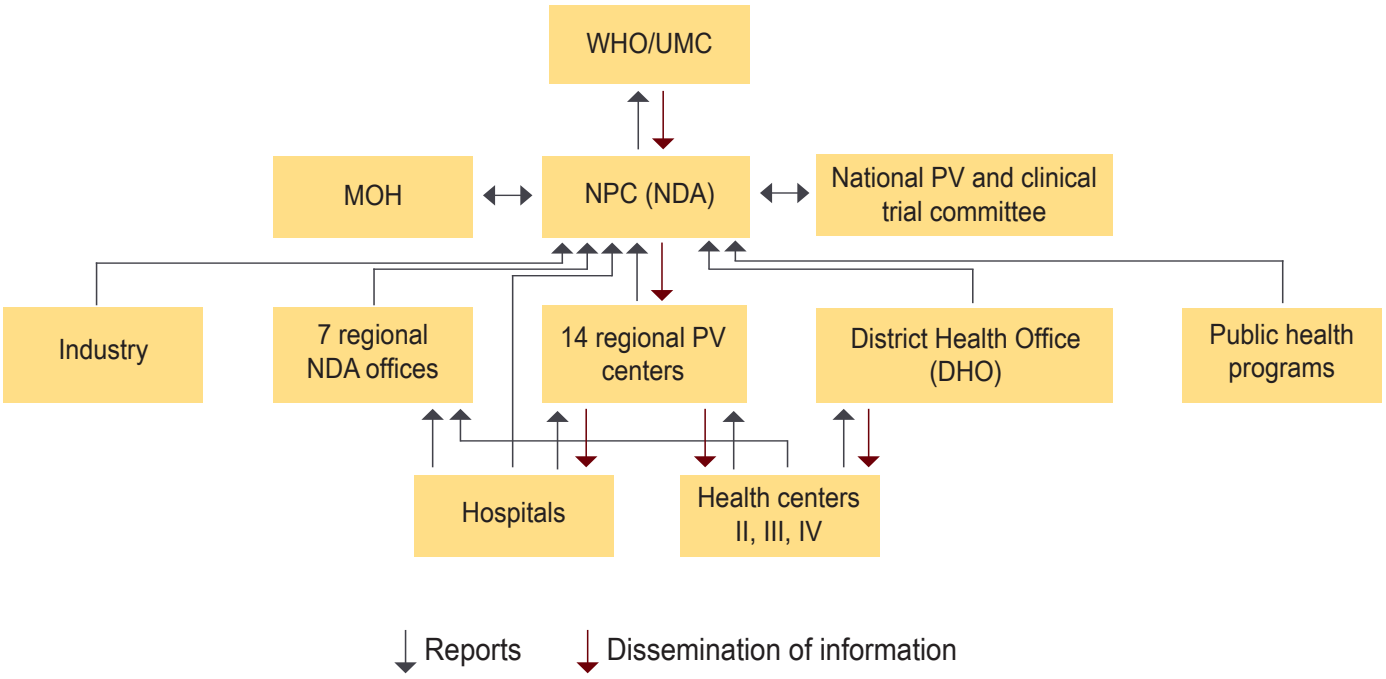
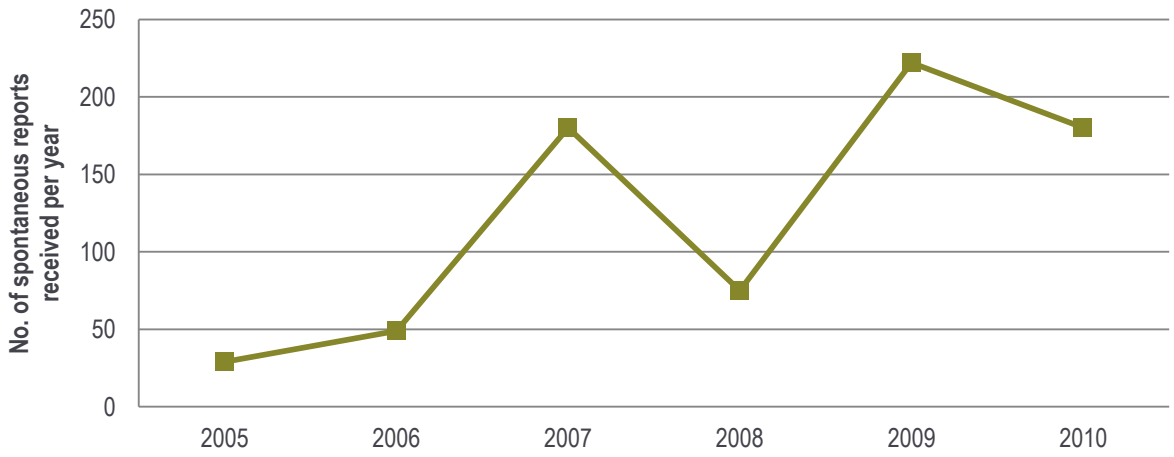


Figure 41. Spontaneous reporting in Uganda



stibogluconate and paramomycin for the treatment of visceral leishmaniasis; searching patient records and the database systematically when there is an important safety issue arising from spontaneous reporting; and working with PHPs and developing partners to conduct active surveillance. There is ongoing CEM of ACTs in pregnancy in collaboration with the NMCP and the Uganda Malaria Surveillance Project and active vaccine surveillance in the Uganda National Expanded Program on Immunization. In addition, strong interest from NTLP and the national AIDS control program to collaborate with the NPC is an opportunity to expand the involvement of PHPs. The NPC is also supporting the National Cancer Institute to develop a guideline for monitoring ADRs and developing report forms specific for highly specialized cancer treatment.

The NPC publishes PV newsletters containing important regulatory decisions, summaries of serious ADR reports received, and safety and efficacy issues identified from external sources. Press releases and safety alerts are also used for dissemination of important risks (box 10). However, effective communication to health care workers and consumers is still a challenge, as it is in many countries.

Although a formal PV system was established relatively recently, the system is well structured with institutional capacity and key components for a functional and efficient system. Next steps will include enforcement of regulation for PV,[196] improved dissemination of information, development of a strategy to coordinate stakeholders and fragmented activities, better utilization of existing capacity (i.e., routine surveillance systems) in PHPs and other established institutions to strengthen signal generation and risk evaluation, and engagement of the private sector, including the pharmaceutical industry, in PV systems.

Table 24. Safety Research in Uganda

Study methodology		Number	PHP area				
			HIV/AIDS	TB	Malaria	Vaccine	Others
Safety studies	Active surveillance	6	2	0	1	1	2
	Active and passive surveillance	1	0	0	1	0	0
Clinical trials	Phase 3	3	1	0	1	0	1
	Phase 4	4	2	0	1	0	1
	Total	14	5	0	4	1	4

Box 10. ADRs to Pethidine

The NPC received four case reports from two physicians in 2010 describing fasciculation in association with the administration of pethidine, an opioid analgesic. Patients who received 100 mg of pethidine (IM) to manage postoperative pain presented fasciculations followed by respiratory depression within approximately 5 minutes of administration. One of the patients progressed to cardiac arrest and recovered after resuscitation. The reporters suspected the quality of the injection, but quality control tests confirmed that the product complied with the quality specification. Inappropriate dosing and administration of pethidine-like opioids can result in respiratory depression, hypotension, fasciculations, and cardiac arrest. The NPC urged health care professionals to closely monitor patients to whom pethidine is administered and report any event to the authority. The NPC communicated the potential risks of medication error in the use of pethidine through the newsletter.

Sources: Interview with drug officer in NDA and the *Pharmacovigilance News*, vol. 5, issue 1, 2011

196 National Drug Authority. 2011. Regulation and strategic plan (draft)

Conclusion

The findings of this study demonstrate that PV activities are already taking place in most SSA countries. Opportunities exist to advance PV systems in these countries with current interest and support from global health initiatives. However, lack of coordination and strategic vision to include all components of PV resulted in a fragmentation of the system and limited capacity to ensure quality, efficacy, and safety of medicines. Greater efforts are needed to add to this effort and to link existing activities together for a comprehensive PV system. Careful strategic planning to incorporate both passive and active approaches and coordinate all stakeholders and their contributions can further enhance the impact of PV and medicine safety systems, and ultimately, improve quality of care and patient safety. Such a strategy should be implemented in a phased approach to meet a country's specific needs and eventually build the countries' own capacity to ensure sustainable development, including dedicated funding from the government. The following are recommended to address identified gaps.

Recommendations

Components of PV

Policy, Law, and Regulation

- **Countries should develop policy and legal frameworks to adequately address medicine safety monitoring.** The lack of relevant policy and regulations in SSA reflects fundamental limitations for enforcing medicine safety monitoring. In particular, lack of legal provision resulted in minimal PV activities in the pharmaceutical industry. Relevant regulations should be developed to mandate the responsibilities of the pharmaceutical industry including mandatory reporting for MAHs and requirements for post-marketing surveillance activities.
- **Countries should develop a comprehensive national guideline for PV.** The study indicates that only 39 percent of SSA countries have national guidelines. A comprehensive PV national guideline is necessary to standardize provision of PV services and processes at all levels of the health system and to coordinate the activities among various stakeholders. The essential components of such documents may include references to policy and legal provisions for PV, scope of PV and medicine safety surveillance systems, roles and responsibilities of all stakeholders, notification system, methods for safety surveillance (including both spontaneous reporting and active surveillance), communication strategy, risk management strategy, and monitoring and evaluation with PV indicators.

System, Structure, and Stakeholder Coordination

- **Countries should develop a strategy to facilitate coordination of PV activities among all stakeholders.** The study showed that the coordination of all stakeholders was weak with limited interactions and collaboration among the stakeholders in most countries. The first step to establish such coordination is to develop a comprehensive mapping of stakeholders with defined roles and responsibilities. In particular, where various players and initiatives, such as PEPFAR, the Global Fund, BMGF, and PMI, are supporting countries to strengthen PV system, effective coordination should be sought to ensure these efforts are complementary and not duplicative.

Signal Generation and Data Management

- **Countries should incorporate active surveillance activities such as registries, sentinel sites, and CEM into the national PV system through close collaboration with research institutions, academia, and technical agencies.** A comprehensive PV system requires both passive and active approaches to evaluate potential problems and provide measures of the level of potential risk. The study found that there is existing capacity to conduct medicine safety research in almost half of SSA countries, although many of these activities are not known to national authorities, and data from these studies are not widely shared. Collaboration among regulatory authorities, academic institutions, and PHPs should be established to leverage the resources, prioritize the safety issues of public health importance, and evaluate the risk of medicines. SSA regional communities can be supported by donors and international technical agencies to develop networks linking research institutions and regulatory authorities. For example, establishment of such a regional network can build on existing efforts to harmonize medicines registration through the African regional economic communities and establish a regional network for medicines research and development.
- **Countries should strengthen routine surveillance of product quality throughout the supply chain by engaging both passive and active approaches.** This can include monitoring quality complaints from spontaneous reports and sampling and testing of products throughout the product life cycle. Another study might be required to provide a more comprehensive overview of product quality monitoring systems including those in the pharmaceutical industry in SSA.

Risk Assessment and Evaluation

- **Technical agencies and more advanced regulators can help countries to develop a standard procedure or operational tool to review, assess, and use safety reports from outside sources for local decision making.** The finding that most countries do not have a systematic approach for processing safety alerts from SRAs, such as FDA or EMA, and global literatures implies missed opportunities to use easily accessible and locally relevant safety data. The capacity of regulatory authorities to routinely scan those safety alerts, evaluate risks and benefits in local markets, and, if necessary, act on them by making regulatory decisions or communicating the risk to health care workers and public should be strengthened.
- **Countries should collaborate with health professional associations and academia to ensure locally relevant PV topics are integrated in pre- and in-service training programs.** PV is not well integrated into training curricula in Africa's medical, pharmacy, nursing, and public health schools; less than half of academic institutions surveyed provide PV-related training. The regulatory authority should collaborate with professional associations, such as pharmacy council, medical association, or nursing association, that oversee the development of standard curricula to ensure key topics related to medicines safety are included in the programs.

Risk Management and Communication

- **Technical agencies and more advanced regulators can support countries to develop and implement a comprehensive risk-mitigation plan targeting high-risk medicines.** The study results indicate that no consolidated or

standardized procedure for risk management was in place even though high-risk medicines are available. SRAs such as EMA and FDA require pharmaceutical companies to submit and implement a set of risk management activities for high-risk medicines. Although such medicines are registered and marketed in African countries, patients are exposed to the identified risks without any safety measures or risk minimization strategies. Pharmaceutical companies should be encouraged to submit and implement risk mitigation strategies at the local level.

- **Strategies for communication and informational exchange should be developed to widely disseminate the safety information and identified risks** to health care workers, the public, and all stakeholders, including regulatory agencies in other countries. With collaboration among regulators to strengthen safety standards, countries can access safer, higher-quality products and enhance economic development through productive industry and a reliable global market for medicines.[197] The study shows that sharing and communicating the safety information was poor in most countries. Various measures including safety newsletters, medicine information bulletins, safety alerts, and press releases can be employed by national PV centers to ensure the effective communication of medicine safety. Also, a web-based platform can be developed to facilitate timely sharing of information in the global supply chain among African countries and between African and northern regulators. Northern regulators such as FDA or EMA can support developing a platform to exchange and communicate safety information with African regulators.

PV in Public Health Programs

- **National PV centers should collaborate with in-country stakeholders to enhance PV activities within the existing surveillance structures of PHPs and health facilities**, for example, incorporating adverse event monitoring into routine disease surveillance, disease registry, and drug resistance monitoring. The findings indicate that PHPs have resources and structures to implement PV activities and provide safety data from treatment of newly employed medicines such as ARVs and ACTs. However, the implementation of PV activities in PHPs and health facilities was inadequate with lack of policy framework, little effort to routinely collect adverse event data, and lack of risk management activities. Strategies should be developed to collate the routinely collected data and share this information with national regulatory authorities so that the PV data can be used to confirm or update standard treatment guidelines and essential medicine lists.

Patient Safety and PV

- **The DTCs should strengthen their capacity to carry out PV activities and use the information to ensure medicine safety at the health-facility level in close collaboration with national PV centers.** The findings indicate that the functions of DTCs to monitor, evaluate, and communicate safety issues in health facilities were poor. DTCs should be supported to carry out PV-related activities, such as encouraging health care workers to report adverse events, identifying high-risk medicines on formularies and monitoring the medicine use, reviewing the safety

197 Deborah M. Author. Securing the Pharmaceutical Supply Chain. Statement before the Committee on Health, Education, Labor, and Pensions, United States Senate. Available from http://www.fda.gov/NewsEvents/Testimony/ucm271073.htm

data on a regular basis, developing a protocol for drug use study or medication error survey, and using the safety information to make decisions.

PV in Pharmaceutical Industry

- **The pharmaceutical industry should be encouraged to take responsibility for ensuring medicine safety in every country where their products are marketed.** The finding indicates that pharmaceutical companies in Africa are not proactive in taking measures to ensure medicine safety. Pharmaceutical companies should be encouraged to report the adverse events to regulatory authorities, monitor product quality and counterfeits, and share the safety data. Regulatory authorities should also require industry to report counterfeiting on products registered in their countries that occurs anywhere in the world. This prompt communication will ensure the global supply chain to be accountable and safe.

Support for Strengthening PV Systems

- **Donors should encourage countries to enhance the capacity of the national system to mobilize financial and human resources to ensure sustainability of the system and its performance.** Many national PV centers are currently supported by donors, nongovernmental organizations, and other development partners. Therefore, financing institutions should develop a plan for gradual transitioning their support to in-country governments and using local resources to support the implementation of medicine safety activities.
- **Donors and other development partners should ensure their efforts are coordinated, and not duplicated, to build or strengthen those national PV programs and effectively address the gaps identified in national PV systems.** The systems classification of 46 countries presenting the current capacity and performance of their PV systems can be a useful tool for designing a customized intervention or strategy to target specific needs of countries that will ultimately lead to strengthening the national PV systems.

Afterword

The assessment of PV systems in SSA countries cannot be done at any time better than now. Although access to medicines is increasing globally, the time to fight the harmful effects of medicine use is now. A PV system should include all entities and resources that protect the public from medicine-related harm, whether in personal health care or public health services. The PV system therefore aims to achieve this protection through efficient and timely identification, collection, and assessment of ADEs and by communicating risks and benefits to support decision making at various levels of the health care system. Every medicinal product, no matter how good its quality, poses a safety challenge. Safety monitoring of medicines is essential for effective use of medicines and providing high-quality health care in any country.

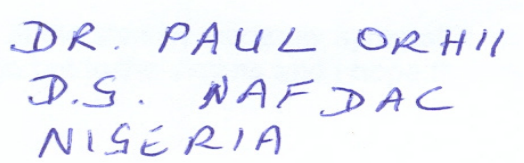
The objectives of this study were well defined and clear. The methodologies x-rayed the different components of PV, vis-a-vis policy, law, and regulation; system, structure, and stakeholder coordination; signal generation and data management; risk assessment and evaluation; risk management and communication; PV in PHPs; patient safety and PV in the pharmaceutical industry.

The results of the study showed that the PV systems in place in most of the 46 SSA countries, in relation to systems capacity and performance, did not meet relevant indicators based on the system classification.

The results of PV activities in PHPs clearly demonstrated little effort by these programs to routinely collate and aggregate adverse events and treatment modification data and share it with PV centers. It is common knowledge that most of the countries surveyed are developing and depend on huge quantities of donated medicines to combat some diseases of public health importance. These PHPs are usually adequately funded and focus on mass distribution of medicines, but have inadequate systems in place to monitor the safety of the medicines they distribute. Strong PV systems can therefore monitor and help ensure the safe use of these medicines that are critical to the success of global PHPs. In their planning phase, global partners must, as a matter of urgency, integrate functional medicine safety systems to monitor the effects of these donated products.

Although the study addressed identified lapses and provided recommendations for strengthening PV systems overall, this aggregated information may not actually

facilitate prompt action by individual countries. Studies and reports are needed to specifically indicate individual country strengths, weaknesses, opportunities, and threats to enable them to develop strategic plans for improvement.



Paul Orhii (Director General NAFDAC)

Annexes

Annex A. Pharmacovigilance Profile[a]

Policy, law, and regulation

Country	National PV policy exists[b] (Year published)	Legal provision for PV exists (Year published)	Legal provision for MAH to report ADR exists (Year published)	Legal provision for MAH to conduct PMS exists (Year published)
Angola	No	No	No	No
Benin	No	No	Yes	No
Botswana	Yes (2002)	No	No	No
Burkina Faso	Yes (2010)	No	Yes	No
Burundi	No	No	No	No
Cameroon	No	No	N/A	N/A
Cape Verde	N/A	N/A	N/A	N/A
Central African Republic	N/A	N/A	N/A	N/A
Chad	N/A	N/A	N/A	N/A
Comoros	N/A	N/A	N/A	N/A
Congo (DRC)	Yes	No	No	No
Congo (Republic)	N/A	N/A	N/A	N/A
Côte d'Ivoire	Yes (2010)	No	Yes (2010)	Yes (2010)
Djibouti	N/A	N/A	N/A	N/A
Equatorial Guinea	N/A	N/A	N/A	N/A
Ethiopia	Yes (2009)	Yes (2009)	Yes	No
Gabon	N/A	N/A	N/A	N/A
Gambia	N/A	N/A	N/A	N/A
Ghana	Yes (2004)	No	No	No
Guinea	Yes (2007)	Yes (1994)	Yes (1994)	Yes (1994)
Guinea-Bissau	N/A	N/A	N/A	N/A
Kenya	No	Yes (2002)	No	No
Lesotho	N/A	N/A	N/A	N/A

[a]All data used for the analysis can be found in the SPS program website available at http://www.msh.org/projects/sps/Resources/FDA-Study-of-Medicines-Safety.cfm. The database contains related policies, laws, regulations, guidelines, tools, SOPs, reports, training materials, key literature, and other relevant documents that have been compiled during the study.

[b]PV policy statements within the NMP or as part of other MoH policy documents

Policy, law, and regulation (continued)

Country	National PV policy exists[b] (Year published)	Legal provision for PV exists (Year published)	Legal provision for MAH to report ADR exists (Year published)	Legal provision for MAH to conduct PMS exists (Year published)
Liberia	N/A	N/A	N/A	N/A
Madagascar	No	No	No	No
Malawi	Yes (2008)	Yes	No	No
Mali	Yes (2008)	Yes (2008)	Yes (2008)	Yes (2008)
Mauritania	N/A	N/A	N/A	N/A
Mauritius	N/A	N/A	N/A	N/A
Mozambique	NO	Yes (2010)	Yes (2010)	No
Namibia	Y (2010)	Y (2003)	Yes	Yes
Niger	N/A	N/A	N/A	N/A
Nigeria	Yes (2005)[c]	Yes (1993)	Yes (draft, 2009)	Yes (draft, 2009)
Rwanda	Yes (2010)	Yes (draft)	No	Yes
Sao Tome e Principe	N/A	N/A	N/A	N/A
Senegal	Yes (2005)	Yes (2009)	Yes (2009)	Yes (2009)
Seychelles	N/A	N/A	N/A	N/A
Sierra Leone	Yes (2010)[d]	N/A	N/A	N/A
South Africa	No	Yes (1997)	Yes (1997)	Yes (1997)
Sudan	Yes (2009)	No	Yes	No
Swaziland	N/A	N/A	N/A	N/A
Tanzania (+Zanzibar)	No	Yes (2003)	No	No
Togo	Yes (2008)	Yes	Yes	No
Uganda	Yes (2002)	No	No	No
Zambia	Yes (1997)	No	No	No
Zimbabwe	Yes (1998)	Yes	No	No

[c]PV biannual plan and guideline used for the National TB Control Program (source: the Global Fund, proposal for Round 9)

[b]The Ministry of Health. National Strategic Plan. 2010.

System, structure, and stakeholders coordination

Country	PV center with a clear mandate, structure, roles, and responsibilities exists	Drug information service exists
Angola	PV unit under MOH; funding from government	Yes, by PV center
Benin	Service l'inspection et pharmacovigilance under NMRA; funding from donor and government	Yes, by DI center in hospitals
Botswana	PV unit under NMRA; funding from government	Yes, by PV center
Burkina Faso	PV center under NMRA; funding from government	Yes, by DI center (CEDIM)
Burundi	PV center under NMRA, no dedicated funding	No
Cameroon	PV center under NMRA; information on funding source not available	N/A
Cape Verde	PV center	N/A
Central African Republic	N/A	N/A
Chad	N/A	N/A
Comoros	N/A	N/A
Congo (DRC)	PV center affiliated with academic institution, funding from donors	Yes, by academic institution
Congo (Republic)	N/A	N/A
Côte d'Ivoire	PV center under NMRA and MOH; funding from government and donors	Yes, by PV center
Djibouti	N/A	N/A
Equatorial Guinea	N/A	N/A
Ethiopia	FMHACA PV center under NMRA; funding from government and NGOs	Yes, by PV center
Gabon	N/A	N/A
Gambia	PV center	N/A
Ghana	PV center under NMRA; funding source not available	Yes, by DI unit in NMRA (limited linkage with PV center)
Guinea	PV center under NMRA and MOH; funding from government and donors	Yes, by PV center
Guinea-Bissau	PV center (affiliation and funding source not available)	N/A
Kenya	PV center under NMRA (PPB); funding from government and donors	Yes, by PV center
Lesotho	N/A	N/A
Liberia	PV center	N/A
Madagascar	PV center under NMRA, funding from government, donors, and PHPs	Yes, by DI unit in NMRA
Malawi	PV center under NMRA, funding from government	Yes, DI center in NMRA
Mali	PV center under MOH, funding from donor and government	Yes, by PV center
Mauritania	PV center	N/A
Mauritius	N/A	N/A
Mozambique	PV center under NMRA, funding from government	Yes, by PV center and academic institution (CIMED)
Namibia	PV center under NMRA, funding from donors and government	Yes, by PV center
Niger	PV center	N/A
Nigeria	PV center under NMRA (NAFDAC); funding from government	Yes, by PV center
Rwanda	PV center under MoH; funding from government and NGO	Yes, by PV center
Sao Tome e Principe	N/A	N/A
Senegal	PV unit under NMRA, funding from government	No

System, structure, and stakeholders coordination (continued)

Country	National PV guideline exists (Year published)	National safety advisory committee exists	Mechanism for coordinating PV activities across all stakeholders exists	WHO membership (Year joined)
Angola	No	No	No	Associate
Benin	No	No	No	Official (2011)
Botswana	Yes (2009)	No	Yes	Official (2009)
Burkina Faso	No	No	No	Official (2010)
Burundi	No	No	No	Associate
Cameroon	N/A	Yes	No	Official (2010)
Cape Verde	N/A	N/A	N/A	Associate
Central African Republic	N/A	N/A	N/A	Non-member
Chad	N/A	N/A	N/A	Non-member
Comoros	N/A	N/A	N/A	Non-member
Congo (DRC)	No	Yes	No	Official (2010)
Congo (Republic)	N/A	N/A	N/A	Non-member
Côte d'Ivoire	Yes (2010)	Yes	No	Official (2010)
Djibouti	N/A	N/A	N/A	Non-member
Equatorial Guinea	N/A	N/A	N/A	Non-member
Ethiopia	Yes (2008)	Yes	Yes	Official (2008)
Gabon	N/A	N/A	N/A	Non-member
Gambia	Yes[6]	Yes[7]	N/A	Associate
Ghana	Yes (2010)	No	Official (2001)	
Guinea	Yes (draft)	No	Yes	Associate
Guinea-Bissau	N/A	N/A	N/A	Associate
Kenya	Yes (2009)	Yes	Yes	Official (2010)
Lesotho	N/A	N/A	N/A	Non-member
Liberia	N/A	N/A	N/A	Associate
Madagascar	No	No	No	Official (2009)
Malawi	Yes (2010)	Yes	Yes	Non-member
Mali	Yes (2008)	Yes	Yes	Official (2011)
Mauritania	N/A	N/A	N/A	Associate
Mauritius	N/A	N/A	N/A	Non-member
Mozambique	Yes (2004)	No	No	Official (2005)
Namibia	Yes (draft)	Yes	Yes	Official (2009)
Niger	N/A	N/A	N/A	Associate
Nigeria	Yes (2008)	Yes	No	Official (2004)
Rwanda	Yes (2011)	No	Yes	Associate
Sao Tome e Principe	N/A	N/A	N/A	Non-member
Senegal	Yes (2010)	Yes	Yes	Official (2009)

System, structure, and stakeholders coordination (continued)

Country	PV center with a clear mandate, structure, roles, and responsibilities exists	Drug information service exists
Seychelles	N/A	N/A
Sierra Leone	PV center under NMRA, funding from donor	Yes, by PV center
South Africa	PV unit under NMRA and The National Adverse Drug Event Monitoring Centre (NADEMC) situated in the University of Cape Town; funding source not available	Yes, by academic institution
Sudan	PV center under NMRA; funding source not available	No
Swaziland	N/A	N/A
Tanzania (+Zanzibar)	PV center under NMRA (TFDA); funding from donor and government	Yes, by PV center
Togo	PV center under NMRA, No dedicated funding for PV	Yes, by PV center
Uganda	PV center under NMRA (with regional PV centers); funding from government	Yes, by PV center
Zambia	PV center under NMRA; funding from donor, government, PHPs and NGO	No
Zimbabwe	PV center under NMRA; funding from donor	No

System, structure, and stakeholders coordination (continued)

Country	National PV guideline exists (Year published)	National safety advisory committee exists	Mechanism for coordinating PV activities across all stakeholders exists	WHO membership (Year joined)
Seychelles	N/A	N/A	N/A	Non-member
Sierra Leone	No	Yes	Yes	Official (2008)
South Africa	Yes (2010)	Yes	Yes	Official (1992)
Sudan	No	No	No	Official (2008)
Swaziland	N/A	N/A	N/A	Non-member
Tanzania (+Zanzibar)	Yes (2010)	Yes	No	Official (1993)
Togo	No	No	Yes	Official (2007)
Uganda	Yes (2009)	Yes	No	Official (2007)
Zambia	Yes (2006)	Yes	Yes	Official (2010)
Zimbabwe	Yes	Yes	Yes	Official (1998)

Signal generation and data management

Country	Coordination and collation of PV data from all sources in the country (see key below)	Spontaneous reporting on ADRs	Spontaneous reporting on product quality	Spontaneous reporting on medication error	Spontaneous reporting on treatment failure
Angola	b	Yes	Yes	Yes	Yes
Benin	b	Yes	No	No	No
Botswana	b	Yes	Yes	No	Yes
Burkina Faso	b	Yes	Yes	No	Yes
Burundi	a	Yes	No	No	No
Cameroon	b	Yes	N/A	N/A	N/A
Cape Verde	N/A	Yes	N/A	N/A	N/A
Central African Republic	N/A	N/A	N/A	N/A	N/A
Chad	N/A	N/A	N/A	N/A	N/A
Comoros	N/A	N/A	N/A	N/A	N/A
Congo (DRC)	b	Yes	No	No	Yes
Congo (Republic)	N/A	N/A	N/A	N/A	N/A
Côte d'Ivoire	a	Yes	Yes	No	No
Djibouti	N/A	N/A	N/A	N/A	N/A
Equatorial Guinea	N/A	N/A	N/A	N/A	N/A
Ethiopia	a	Yes	Yes	Yes	Yes
Gabon	N/A	N/A	N/A	N/A	N/A
Gambia	N/A	Yes	N/A	N/A	N/A
Ghana	c	Yes	Yes	Yes	Yes
Guinea	b	Yes	Yes	Yes	Yes
Guinea-Bissau	N/A	N/A	N/A	N/A	N/A
Kenya	b	Yes	Yes	No	No
Lesotho	N/A	N/A	N/A	N/A	N/A

a) No database

b) Database exists, containing partial sources of information

c) Database exists, containing all sources of information

Signal generation and data management (continued)

Country	Coordination and collation of PV data from all sources in the country (see key below)	Spontaneous reporting on ADRs	Spontaneous reporting on product quality	Spontaneous reporting on medication error	Spontaneous reporting on treatment failure
Liberia	N/A	Yes	N/A	N/A	N/A
Madagascar	b	Yes	Yes	Yes	Yes
Malawi	a	Yes	Yes	Yes	Yes
Mali	b	Yes	Yes	Yes	Yes
Mauritania	N/A	N/A	N/A	N/A	N/A
Mauritius	N/A	Yes	N/A	N/A	N/A
Mozambique	b	Yes	Yes	Yes	Yes
Namibia	b	Yes	Yes	Yes	Yes
Niger	N/A	Yes	N/A	N/A	N/A
Nigeria	c	Yes	Yes	Yes	No
Rwanda	b	Yes	Yes	Yes	Yes
Sao Tome e Principe	N/A	N/A	N/A	N/A	N/A
Senegal	c	Yes	Yes	Yes	Yes
Seychelles	N/A	N/A	N/A	N/A	N/A
Sierra Leone	b	Yes	N/A	N/A	N/A
South Africa	c	Yes	Yes	No	Yes
Sudan	a	Yes	Yes	No	Yes
Swaziland	N/A	N/A	N/A	N/A	N/A
Tanzania (+Zanzibar)	b	Yes	Yes	Yes	Yes
Togo	b	Yes	Yes	Yes	Yes
Uganda	b	Yes	Yes	Yes	Yes
Zambia	b	Yes	Yes	Yes	Yes
Zimbabwe	b	Yes	Yes	Yes	No

a) No database

b) Database exists, containing partial sources of information

c) Database exists, containing all sources of information

Risk assessment and evaluation

Country	No. of ADR report per million population in 2010	Survey on quality of pharmaceutical products carried out in the last 5 years (No. of surveys)	No. of medicine use and medication error studies in the last 5 years	No. of active surveillance activities in the last 5 years
Angola	0	0	0	0
Benin	0	Yes (N/A)	0	0
Botswana	32	0	1	1
Burkina Faso	131	Yes (1+)	0	4
Burundi	0	0	0	0
Cameroon	N/A	Yes (1+)	0	3
Cape Verde	N/A	N/A	0	0
Central African Republic	N/A	N/A	0	0
Chad	N/A	N/A	0	0
Comoros	N/A	N/A	0	0
Congo (DRC)	2	0	0	3
Congo (Republic)	N/A	N/A	0	0
Côte d'Ivoire	0	Yes (N/A)	0	5
Djibouti	N/A	N/A	0	0
Equatorial Guinea	N/A	N/A	0	0
Ethiopia	2	Yes (3)	5	1
Gabon	N/A	N/A	0	1
Gambia	N/A	N/A	0	0
Ghana	20	Yes (1+)	3	52
Guinea	3	Yes (N/A)	0	2
Guinea-Bissau	N/A	N/A	0	2
Kenya	15	Yes (9)	1	5
Lesotho	N/A	N/A	0	0
Liberia	N/A	N/A	1	0

Risk assessment and evaluation (continued)

Country	No. of ADR report per million population in 2010	Survey on quality of pharmaceutical products carried out in the last 5 years (No. of surveys)	No. of medicine use and medication error studies in the last 5 years	No. of active surveillance activities in the last 5 years
Madagascar	12	Yes (1+)	0	0
Malawi	1	Yes (N/A)	2	3
Mali	22	Yes (43)	2	5
Mauritania	N/A	N/A	0	0
Mauritius	N/A	N/A	0	0
Mozambique	2	0	0	1
Namibia	135	0	0	1
Niger	N/A	N/A	0	0
Nigeria	34	Yes (2)	10	7
Rwanda	0	0	0	2
Sao Tome e Principe	N/A	N/A	0	0
Senegal	10	Yes (1+)	0	4
Seychelles	N/A	N/A	0	0
Sierra Leone	N/A	0	0	0
South Africa	N/A	Yes (N/A)	7	49
Sudan	0	0	3	0
Swaziland	N/A	N/A	0	0
Tanzania (+Zanzibar)	3	Yes (2)	1	10
Togo	N/A	0	0	3
Uganda	6	Yes (1+)	3	11
Zambia	13	Yes (N/A)	0	2
Zimbabwe	5	0	6	3

Risk management and communication*

Country	No. of medicines safety newsletters or bulletins published	% of medicines sampled that passed product quality test	Mitigation plan for high-risk medicines in place	No. of locally relevant safety issues identified and acted on from outside sources	No. of public education activities on ADRs and medicine safety	No. of safety alerts distributed	No. of regulatory actions taken (see key below)
Angola	None exist	N/A	No	4	N/A	4	2 (c, d)
Benin	None exist	N/A	No	0	N/A	0	None
Botswana	None exist	N/A	No	0	N/A	0	None
Burkina Faso	None exist	88%	No	5	0	6	3 (f)
Burundi	N/A	N/A	No	0	0	0	None
Cameroon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cape Verde	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Central African Republic	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chad	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Comoros	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Congo (DRC)	1 published (monthly)	N/A	No	0	0	0	None
Congo (Republic)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Côte d'Ivoire	1 published (2 planned)	N/A	No	2	N/A	2	None
Djibouti	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Equatorial Guinea	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ethiopia	2 published (2 planned)	N/A	No	1	N/A	5	5 (c, d)
Gabon	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gambia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ghana	None exist	66%	No	2	0	4	2 (a, f)
Guinea	None exist	N/A	No	0	0	0	0
Guinea-Bissau	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kenya	1 published (2 planned)	97%	Yes (opioid analgesics and anticoagulants)	12	10	15	12 (b, d, f, g)
Lesotho	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Liberia	N/A	N/A	N/A	N/A	N/A	N/A	N/A

*These are the results of risk management and communication activities in 2010

a) Label changes/boxed warning
b) Treatment guidelines, medicine formulary, or essential medicine list changes
c) MoH memo or circular referencing safety data
d) Product recalls
e) Withdrawal of product license
f) Suspension of marketing authorization
g) Risk management activities recommended because of new safety data

Risk management and communication* (continued)

Country	No. of medicines safety newsletters or bulletins published	% of medicines sampled that passed product quality test	Mitigation plan for high-risk medicines in place	No. of locally relevant safety issues identified and acted on from outside sources	No. of public education activities on ADRs and medicine safety	No. of safety alerts distributed	No. of regulatory actions taken (see key below)
Madagascar	None exist	N/A	No	0	0	0	NONE
Malawi	None exist	N/A	No	2	N/A	3	3 (a, c, d)
Mali	None exist	N/A	No	0	N/A	0	None
Mauritania	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mauritius	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mozambique	None exist	N/A	No	7	N/A	4	11 (a, d, f)
Namibia	3 published (4 planned)	N/A	No	35	N/A	36	2 (e, g)
Niger	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nigeria	3 published (4 planned)	90%	No	7	1	10	3 (a, e, g)
Rwanda	None exist	N/A	No	0	N/A	0	3 (c, d, g)
Sao Tome e Principe	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Senegal	1 published (4 planned)	57%	No	2	0	8	4 (a,d,f)
Seychelles	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sierra Leone	N/A	N/A	N/A	N/A	N/A	N/A	N/A
South Africa	N/A	N/A	N/A	1	N/A	1	1(e)
Sudan	None exist	N/A	No	1	N/A	0	1 (d, f)
Swaziland	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tanzania (+Zanzibar)	None exist	90%	Yes (controlled drugs and anticancer drugs)	3	11	3	3 (e, g)
Togo	None published (quarterly)	N/A	N/A	0	N/A	0	None
Uganda	2 published (4 planned)	86%	Yes (injection, opioid analgesics)	10	2	15	5 (b, c, d, f)
Zambia	0 published (quarterly)	N/A	N/A	0	N/A	0	None
Zimbabwe	None exist	N/A	N/A	5	N/A	5	2 (b, c, d)

*These are the results of risk management and communication activities in 2010

a) Label changes/boxed warning
b) Treatment guidelines, medicine formulary, or essential medicine list changes
c) MoH memo or circular referencing safety data
d) Product recalls
e) Withdrawal of product license
f) Suspension of marketing authorization
g) Risk management activities recommended because of new safety data

Annex B. Mapping of Institutions Working Toward Strengthening PV in SSA

Stake-holders	Policy, law, and regulation		Systems, structures, and stakeholder coordination			
	Development/ review of policies and guidelines	Development/ review/ monitoring compliance to regulation	Strengthen organiza-tional structures	Stakeholder coordination	Provide PV-related training	Provide funding/ advocacy
Financing institutions						
Global Fund to Fight AIDS, Tuberculosis and Malaria	■		■	■		■
USAID				■		■
BMGF			■	■		■
European Comm.				■		■
UNITAID						■
GAVI			■	■		■
Technical and partnership programs						
WHO	■	■	■	■	■	■
Uppsala Monitoring Centre	■		■		■	■
MSH	■	■	■		■	■
USP (USAID-funded PQM program)		■				
Intl. Soc. of Pharmacovigilance					■	
Council for Intl. Organizations of Medical Sciences	■					
ICH	■					
Brighton Collaboration						
Medicines for Malaria Venture						
Médicines Sans Frontièrs						■
Intl. Epidemiologic Database to Evaluate AIDS						
Intl. Pharmaceutical Federation					■	
Forum for Collaborative HIV Research				■		
Drugs for Neglected Diseases Initiative						
Disease-Oriented Partnership Programs (i.e. PMI, PEPFAR, RBM, Stop TB, etc.)	■					■
Regional institutions and region-focused disease program						
WHO Collaborating Centre for Advocacy and Training in PV (UMC-Africa)			■		■	
INESS						
West Africa Network for Monitoring Antimalarial Treatment						

Mapping of Institutions Working Toward Strengthening PV in SSA (continued)

Stake-holders	Signal generation and data management			Risk assessment and evaluation		
	Strengthen ADR reporting	Strengthen other adverse events reporting	Data management	Active surveillance	Vaccine surveillance	Other risk evaluation efforts
Financing institutions						
Global Fund to Fight AIDS, Tuberculosis and Malaria						
USAID						
BMGF				■	■	
European Comm.				■	■	
UNITAID						
GAVI					■	
Technical and partnership programs						
WHO	■	■	■	■	■	■
Uppsala Monitoring Centre	■	■	■	■	■	
MSH	■	■	■	■	■	■
USP (USAID-funded PQM program)		■				
Intl. Soc. of Pharmacovigilance						■
Council for Intl. Organizations of Medical Sciences			■			
ICH						
Brighton Collaboration	■				■	
Medicines for Malaria Venture				■		
Médicines Sans Frontièrs	■			■		
Intl. Epidemiologic Database to Evaluate AIDS				■		
Intl. Pharmaceutical Federation	■					
Forum for Collaborative HIV Research				■		
Drugs for Neglected Diseases Initiative				■		
Disease-Oriented Partnership Programs (i.e. PMI, PEPFAR, RBM, Stop TB, etc.)	■			■		
Regional institutions and region-focused disease program						
WHO Collaborating Centre for Advocacy and Training in PV (UMC-Africa)				■		
INESS				■		
West Africa Network for Monitoring Antimalarial Treatment	■					

Mapping of Institutions Working Toward Strengthening PV in SSA (continued)

Stake-holders	Risk management and communication		
	Develop risk management strategies	Consumer involvement	Risk communication
Financing institutions			
Global Fund to Fight AIDS, Tuberculosis and Malaria			
USAID			
BMGF			
European Comm.		■	
UNITAID			
GAVI			
Technical and partnership programs			
WHO	■		■
Uppsala Monitoring Centre			■
MSH	■		■
USP (USAID-funded PQM program)			
Intl. Soc. of Pharmacovigilance			
Council for Intl. Organizations of Medical Sciences	■		
ICH			
Brighton Collaboration			
Medicines for Malaria Venture			
Médicines Sans Frontièrs			■
Intl. Epidemiologic Database to Evaluate AIDS			
Intl. Pharmaceutical Federation			
Forum for Collaborative HIV Research			
Drugs for Neglected Diseases Initiative			
Disease-Oriented Partnership Programs (i.e. PMI, PEPFAR, RBM, Stop TB, etc.)			
Regional institutions and region-focused disease program			
WHO Collaborating Centre for Advocacy and Training in PV (UMC-Africa)			
INESS			
West Africa Network for Monitoring Antimalarial Treatment			

Annex C. Glossary

Active surveillance: The collection of case safety information as a continuous, preorganized process. It includes a wide range of active approaches to detect and evaluate risks, such as cohort event monitoring, registries, sentinel sites, epidemiological studies (case control study, cohort study, cross sectional study), and phase 4 clinical trials.

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. It may be due to poor product quality, medication error, or known or unknown pharmacological properties.

Adverse drug reaction (ADR): A response to a drug which is noxious and unintended and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Bayesian Confidence Propagation Neural Network: Automated data mining program used by the Uppsala Monitoring Centre. This produces information component values for drug-event combinations. These can be plotted as graphs over time to examine any trend. A positive signal will have information component values that become more significant over time as more cases are included.

Case control study: Study that identifies a group of persons who experienced the unintended drug effect of interest (cases) and a suitable comparison group of people without the unintended effect (control). The relationship of a drug to the drug event is examined by comparing the cases and control with regards to how frequently the drug is present.

Causality assessment: The evaluation of the likelihood that a medicine was the causative agent of an observed adverse event. Causality assessment is usually made according to established algorithms.

Clinical trial: A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) to discover or verify the effects of or identify any adverse reaction to investigational products, or to study the absorption, distribution, metabolism, and excretion of the products with the objective of ascertaining their efficacy and safety.

Cohort event monitoring (CEM): A surveillance method that requests prescribers to report all observed events, regardless of whether or not they are suspected ADRs, for identified patients receiving a specific drug; also called prescription event monitoring.

Counterfeit medicines: Products that are deliberately and fraudulently mislabeled with respect to identity and/or source.

Drug use study: A program to review medicine prescribing, dispensing, or patient use of medicines.

High-risk medicines: Those medicines that have a heightened risk of causing significant or catastrophic harm when used in error.

Individual case safety report: A report that contains information describing a suspected ADR related to the administration of one or more medicinal products to an individual patient.

Medication errors: Any preventable event that may cause or lead to inappropriate medication use or patient harm while medication is in the control of the health care professional, patient, or consumer.

Medical Dictionary for Regulatory Activities (MedDRA): A medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

Pharmacoepidemiology: Study of the use and effects of drugs in large populations.

Pharmacovigilance (PV)/medicine safety: The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems. The aims of PV are early detection of hitherto unknown adverse reactions and interactions, detect increases in frequency of known adverse reactions, identify risk factors and possible mechanisms underlying adverse reactions, and estimate quantitative aspects of benefit/risk analysis, and disseminate information needed to improve drug prescribing and regulation. The scope of PV includes adverse reactions, medication use errors, product quality complaints, and lack of efficacy.

Pharmacovigilance system: PV systems should include all entities and resources that protect the public from medicines-related harm, whether in personal health care or public health services. It addresses the need for both active and passive approaches to identify and assess medicines-related problems, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of PV activities at all levels of the health system.

Post-marketing surveillance: The systematic process of monitoring the use of medical products after a product has been approved. PV is part of post-market surveillance.

Product quality survey: A study that has sampled and tested the quality of medicines according to a standard procedure of quality surveillance.

Quality assurance: An organized arrangement (processes and systems) of all elements that influence the quality of the product. It involves inspection of compliance with Good Manufacturing Practices, assessment of documentation on product quality submitted by the manufacturer, sampling and testing of medicines from the market or different entry points, and systematic evaluation of reported quality problems through the PV system.

Record linkage: Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Registries: A list of patients presenting with the same characteristic(s). This characteristic can be pregnancy (pregnancy registry), a disease (disease registry), or a specific exposure (drug registry).

Risk management: A set of activities designed to identify, characterize, prevent, or minimize risks related to the medicine; to assess the effectiveness of those interventions; and to communicate those risks to patients and health care providers.

Sentinel sites: The selected sites that can provide complete and accurate information on reported adverse events, such as data from specific patient subgroups.

Serious adverse events: Any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.

Signal: Defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" that may be a new adverse effect or a change in the character or frequency of an ADR that is already known.

Spontaneous reporting: Unsolicited communication by health care professionals or consumers that describes one or more suspected adverse events in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.

Stringent regulatory authorities: Members, observers, or associates of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Substandard medicines: Products whose composition and ingredients do not meet the correct scientific specifications and that are consequently ineffective and often dangerous to the patient.

Treatment failure: Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

VigiBase: Name for the WHO International Adverse Drug Reaction Database.

VigiFlow: A sophisticated case report management system created by the Uppsala Monitoring Centre for the submission of spontaneous ADR reports.

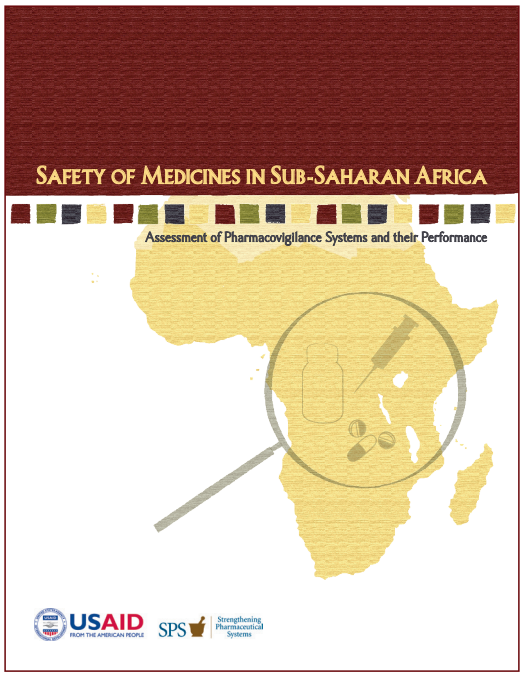
WHO-ART: WHO terminology for coding clinical information in relation to drug therapy, used throughout the WHO Programme for International Drug Monitoring.

Regulatory authorities have responsibility beyond getting the product to the market. The lip service that is currently paid to post-marketing surveillance is well documented by this report…

Margareth Ndomondo-Sigonda, African Medicines Regulator

Patient safety should be at the center of all we do. This study has highlighted how far we are from that goal.... But it is not without hope. In its recommended strategies, the report shows opportunities exist for everyone to act. What is needed is the will to act now!

Eva Ombaka, Visiting Lecturer, St. John's University, Tanzania, and formerly with the Ecumenical Pharmaceutical Network



The result of the study clearly showed little efforts by public health programs. Monitoring and ensuring the safe use of medicines are critical to the success of these programs. Global partners must, as a matter of urgency, integrate in their planning phase, functional medicine safety systems to monitor the effects of donated products.

Paul Orhii, Director General, National Agency for Food and Drug Administration and Control, Nigeria

Pharmacovigilance is a critical component of health systems and of importance to all stakeholders, regulators, industry, health workers, and patients — for whom it may well be a maatter of life and death.

Alex Dodoo, Director, WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana