Development of a pharmacovigilance system in a resource-limited country: the experience of the Democratic Republic of Congo

Didier Nzolo, Andrea Kuemmerle, Yves Lula, Nsengi Ntamabyaliro, Aline Engo, Bibiche Mvete, Jerry Liwono, Mariano Lusakibanza, Gauthier Mesia, Christian Burri, Samuel Mampunza and Gaston Tona

Abstract: Implementation of pharmacovigilance (PV) systems in resource-limited countries is a real endeavor. Despite country- and continent-specific challenges, the Democratic Republic of the Congo (DRC) has been able to develop one of the most active PV systems in the sub-Saharan Africa. The World Health Organization (WHO) regional Office identified the DRC experience to set up a PV system for antimalarial drugs safety monitoring as a ‘best practice’ that needed to be documented in order to help DRC improve its PV system and to be scaled up in other African countries. In response to the WHO request, a best practices and bottlenecks analysis was conducted in 2015. This analysis was updated in 2018 in the light of the minimum requirements of the WHO to set up a PV system taking into account other guidance for PV systems. The following themes were retained for analysis: (1) creation of the national PV center; (2) implementation of PV in the health system; (3) data collection and analysis; (4) collaboration with public health programs; (5) collaboration with the National Regulatory Authority. Lessons learnt from the DRC experience show that it is possible to implement PV systems in order to promote patients’ safety in resource limited sub-Saharan African countries with no guaranteed funding. The ability of national PV centers to collaborate with Public health stakeholders, including public health authorities at all levels as well as public health programs, and to use existing health information systems are considered the main key to success and may substantially reduce the cost of PV activities.

Keywords: Africa, best practices, Democratic Republic of Congo, low- and middle-income country, pharmacovigilance, resource-limited country

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Introduction
Pharmacovigilance (PV) is defined by the World Health Organization (WHO) as the ‘science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems’.1 According to the WHO, it is necessary for countries to have PV systems in order ‘to prevent drug-related adverse effects in humans, ensure patient safety and promote the rational use of drugs’.2 Since the thalidomide tragedy in the 1960s, developed countries have started implementing systems for safety monitoring of various medicinal products used for the subject’s well-being. At the time, PV was considered as a luxury system affordable only to the developed world. Over time, it was convened that PV should be extended even to developing countries for public health and for rational, safe, and cost-effective use of medicines.3 The necessity of implementing PV systems...
in the developing world was underpinned by high global burden of infectious diseases, increasing proportion of noncommunicable diseases, and advocacy for access to existing pharmaceutical drugs and for the development of new drugs or vaccines for disease control.4–6 Unfortunately, in low-income countries, PV is being implemented in health systems with poor infrastructure, unreliable supply and quality of medicines, lack of adequately trained health staffs, limited access to health care services and communication, poor awareness and interest of national stakeholders in drug safety, poor regulatory capacity and authorities, limited funding of health related concerns by national authorities.5,7–9 All these constitute challenges that make development of PV systems in developing countries uncertain. As an example, the contribution of the African continent in the WHO global database (VigiBase™) is <1%, with >50% coming from South Africa, Egypt, Morocco, and Tunisia.10 Table 1 provides the World Bank classification of sub-Saharan African countries by income.

Despite all the challenges, some limited-resource sub-Saharan African countries have been able to set up functional PV systems. The goal of this article is to share the experience of the Democratic Republic of Congo (DRC) in developing its own PV System and to put its best practices and bottlenecks into a broader perspective.

**The DRC health care system**

DRC is the largest sub-Saharan African country located in Central Africa with 2,345,409 km², a

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<th>Table 1. Classification of sub-Saharan African countries by income.</th>
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GNI, gross national income; DRC, Democratic Republic of Congo.
population estimated to 77.8 million inhabitants in 2012,\(^1\) and sharing borders with nine countries (Angola, Burundi, Central African Republic, Republic of Congo, Rwanda, South Sudan, Tanzania, Uganda, and Zambia). The health system is divided into the national level, 26 provinces (intermediate level), and 518 health zones (operational level), each covering a population of 100,000–150,000 inhabitants on average. DRC has one of the poorest populations worldwide with a human development index of 0.457 (176th out of 189 countries and territories worldwide).\(^1\) The DRC is crossed by many rivers, is the territory of deep rainforests and savannahs and has one of the poorest road systems, with more than half of the territory reachable only by airplane from Kinshasa, the capital city. This overall poor infrastructure and the climate with heavy rainfalls and floods make access very difficult or sometimes impossible to health care services. In addition, DRC has been the theater of armed conflicts for almost 20 years creating instability and insecurity.

**Overview of the DRC national PV system**

The DRC National PV Center (CNPV) was created in 2009 and is located at the University of Kinshasa, in the Unit of Clinical Pharmacology and Pharmacovigilance. Creation of the CNPV was motivated by WHO recommendation to the DRC ministry of health to set up a PV system to promote patients’ safety, with an emphasis on monitoring the safety profile of new drugs or drug combinations introduced for the treatment of high-burden public health diseases such as HIV–AIDS, malaria, and tuberculosis. The Unit of Clinical Pharmacology and Pharmacovigilance comprises 21 medical doctors and 9 pharmacists working at a central level. Nowadays the CNPV is active in 115 out of 518 health zones with 4 regional PV centers already implemented. Individual case safety reports (ICSRs) are issued at health facility levels and are sent up to the CNPV where data entry is performed (Figure 1). Despite all the challenges experienced in the country, DRC has one of the most active PV systems in Africa with >15,000 ICSRs reported to the WHO ICSR global database (VigiBase\textsuperscript{TM}) to date.

**Best practices and bottleneck analysis**

In 2015, the WHO regional office identified the DRC experience to set up a PV system for
antimalarial drugs safety monitoring as a ‘best practice’ that needed to be documented in order to help DRC improve its PV system and to be scaled up in other African countries, with an emphasis on Central African countries. In response to the WHO request, a best practices and bottleneck analysis was conducted. It was based on a systemic documentary review of the processes that were implemented to set up the PV system in DRC. Best practices were considered as the achievements and strategies that helped DRC to implement its PV system in comparison with other neighboring countries in Central Africa. The report, written in French, was submitted to the WHO but never published. For the purpose of this article, we reviewed the finding of this report, and updated them with new experience acquired from 2015 to 2018. The selection of the main themes for the assessment of the DRC PV system was mainly performed in light of the minimum requirements of the WHO to set up a PV system.\(^2\) Taking also into account other guidance for PV systems,\(^1,9,13,14\) we retained the following themes for analysis:

1. creation of the national PV center.
2. implementation of PV in the health system.
3. data collection and analysis.
4. collaboration with public health programs (PHPs).
5. collaboration with the National Regulatory Authority.

**Creation of the national PV center**

*Best practices.* The CNPV has been installed at the University of Kinshasa, in the Unit of Clinical Pharmacology and Pharmacovigilance, on the basis of an agreement between the Ministry of Health and the Ministry of Education in DRC. The Unit of Clinical Pharmacology and Pharmacovigilance comprises pharmacists and medical doctors already familiar with drug-related problems. Among medical doctors, the CNPV can benefit from the knowledge and experience of general practitioners, pediatricians, internal medicine physicians, gynecologists, psychiatrists, etc. to solve drug-related issues.

The location at the university offers a broad range of opportunities for capacity building in a low-resource setting. Out of the available PV short courses in Morocco (in French), Ghana, and the Uppsala Monitoring Center (UMC), teaching and masters courses in PV, pharmacoepidemiology and clinical trials as well as PhDs in drug- and vaccine-related problems strengthen knowledge with up-to-date literature and motivate potential future researchers to collaborate with other academic institutions. In addition, it allows scientific exchange and even fellowships in pharmaceutical companies and in research-oriented institutions such as Medicines for Malaria Venture (MMV) and the Swiss Tropical and Public Health Institute.

Since its creation, the national PV center could interact with other international PV institutions. Collaboration with the WHO Collaborating Center for International Drug Monitoring, namely the UMC, and membership in the WHO Programme for International Drug Monitoring, the International Society of Pharmacovigilance (ISOP), as well as the International Society of Pharmacoepidemiology (ISPE) allowed DRC PV staff to interact with other national PV centers and other researchers involved in drug safety. Participation in annual meetings and conferences allowed experience to be shared with and knowledge to be learned from other national PV systems. The Unit of Clinical Pharmacology and Pharmacovigilance is also part of consortia and allows CNPV staff to be involved in clinical trials where they acquire new knowledge and experience about PV of drugs in development. Among these consortia are the Alliance for Clinical Research and Clinical Epidemiology in the DRC (ARCEAU), the Central Africa Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM), and PAmoja TuLinde Maisha (PALM).

*Bottlenecks.* The main challenge of localization of the CNPV at the university resulted from a historic poor interaction between the Ministry of Health and universities in DRC. Public health policies and Ministry of Health decisions are mostly led by WHO recommendation and driven by donors’ requirements. These policies and decisions are often poorly informed by the evidences provided by the universities, which is based on population data and clinical researches conducted in DRC. Consequently, for several years, the policy of the CNPV was driven more by the aim of publishing data for career development than by
the aim of providing evidence-based data for decision making in order to prevent and solve drug- or vaccine-related problems.

Implementation of PV in the health system

**Best practices.** Strategies adopted by the CNPV to implement adverse events spontaneous reporting system in the DRC health system included: (1) 5 days training of PV focal points from national health institutions, PHPs, and general referral hospitals; (2) 2 hours sensitization sessions of health care providers from public and private health facilities when key information in PV are provided; (3) additional training to set up drug and therapeutic committees in charge of analyzing drug- and vaccine-related problems arising in general referral hospitals at provincial level. A PV lesson has been included in the pharmacology course provided to students in medicine, pharmacy, and dentistry schools, making PV part of the student curriculum.

In addition to training and sensitization, supervision visits were used as a strategy to keep the trained and sensitized stakeholders aware of the PV system, to stimulate the reporting of adverse drug reactions, and to maintain PV activities through the focal points. Supervisions were implemented in a context where health care providers are very busy dealing with the collection of many indicators meant to inform different donors of the DRC public health system.

Implementation of a drug therapeutics committee was used as a starting point for the implementation of provincial PV centers. The goal of provincial PV centers was to implement PV activities, including training, sensitization, supervisions and data collection at the provincial level, starting with selected health facilities.

**Bottlenecks.** The lack of funding was the main obstacles to the nationwide implementation of the PV system by the CNPV. Even though funding could be obtained from different donors such as the WHO, Global Funds, Management System of Health (MSH), and Save the Children, they could only fund the implementation of PV in limited number of health facilities, health zones, and provinces. The lack of funding also limited the ability of provincial PV centers to implement the system in their provinces, which resulted in provincial PV center activities restricted to few health facilities. In addition, there was a poor response from focal points from PHPs and public health authorities compared with health care providers, which led to a direct interaction between national/provincial PV centers and health care providers. This resulted in poor involvement of the health authorities from the operational and intermediate level in PV activities.

Data collection and analysis

**Best practices.** The CNPV uses several strategies to collect ICSRs to be entered into the national database for further analysis.

Spontaneous reporting of adverse events by health care providers trained or sensitized in PV is the main source of ICSRs for the DRC PV system. A validated ICSR form is used to report adverse events experienced by patients following use of medicinal products. ICSR forms are filled in by health care providers when patients complain of adverse events following medication or vaccination. ICSRs reported by health care providers are collected directly by CNPV staff during supervisions. Funders involved in PV activities in provinces are also used as channel for transmission of ICSRs from health facilities to CNPV. They participate either by providing Internet access to our provincial focal points, or by carrying the reports under closed cover from the provinces to the CNPV. Spontaneous reporting of adverse events is enhanced by feedback provided by the CNPV to health care providers, as well as technical support for case management of adverse events. For a short period, a system of adverse drug reaction reporting through mobile phone was implemented in 50 out of 518 health zones. It consisted of the use of a closed user group and an electronic ICSR form through a software called Hagenia. ICSRs were sent from the field using the short message system (SMS). A gateway allowed reception of ICSRs through the internet at national level and feedback from the CNPV was sent through SMS to health care providers on a timely manner. The system was designed to capture ICSRs from remote areas with poor access and network coverage as well as to provide support to health care providers for case management and rational use of drugs.
Enhanced spontaneous reporting at the community level was implemented during mass vaccination campaigns in Kinshasa. This allowed discussions about vaccines and adverse events following immunization to be had with the population, to make thousands of people aware of an existing PV system and to collect a huge number of ICSRs. In a country where illiteracy is a concern, this was considered as an alternative to patient reporting.15,16

Active PV was used to implement safety monitoring of some drugs such antimalarial and antituberculosis drugs through cohort event monitoring and allowed the collection of more accurate data necessary to establish the safety profile of drugs on the market based on the incidence of adverse events. Additional research such as drug utilization studies allowed new sources of data to be established such as patient files or hospital registries.17

The DRC PV center opted for the software VigiFlow® to enter the data into its database and to share PV data in the global ICSR database, VigiBase™. To ensure good quality data, the CNPV has implemented a two-step process: data entry in VigiFlow® is performed by junior staff whereas data check and commitment to VigiBase™ is performed by senior staff.18 Safety data are further visualized using VigiLyze or extracted as Excel spreadsheets for further analysis.

First analyses of collected data allowed the most reported adverse events for most frequently used drugs and vaccines in DRC to be determined. These results were presented at international conferences such as the ISOP, and annual meetings, but also published in peer-reviewed journals, which raised awareness about the DRC PV system.

Furthermore, with the huge amount of data, a signal detection system was put in place and allowed some possible quantitative signals to be detected and then submitted to the national PV committee. Signal detection activities started after UMC made its short course available. It was mainly done using the data mining tools in VigiLyze. The new signal detection system led the CNPV to design new strategies to improve the quantity and quality of data collection in order to reduce some biases in quantitative signal detection, to detect more signals, and to efficiently use its database for signal evaluation.

**Bottlenecks.** There is limited capacity of the CNPV to organize supervisions for data collection on a continuous basis. Supervisions are usually fund-driven and stop when funding stops, especially in health facilities located in provinces. When supervisions stop, it happens that health care providers continue to detect adverse events, but do not find the way to send ICSRs to the CNPV. Even data collection through Hagenia software, which covered almost 10% of health zones stopped as soon as the funding stopped. Overall, all funding gathered by the CNPV to implement the PV system since its creation has allowed covering <25% of health zones yet. In addition, signal detection activities, which have no funding, are threatened by several other funded activities, which limit provision of evidences for decision-making by the national regulatory authority.

**Collaboration with PHPs**

**Best practices.** The CNPV has a long history of collaboration with PHPs in DRC for collection, collation, and analysis of safety data. Currently, PV is included in the guideline and in the training modules of PHPs such as the National Immunization Program, the Malaria Control Program, the Tuberculosis Control Program, etc. Some PHPs incorporate PV as part of their activities. They organize data collection from the field themselves and only bring the ICSRs to the CNPV for data entry into the national database and data analysis. This is the case for the Onchocerciasis and the Human African Trypanosomiasis Control Programs. Other PHPs such as the Malaria Control Program leave the organization of data collection, collation, and analysis to the CNPV and only receive safety reports based on CNPV activities. To optimize collaboration with PHPs, the CNPV has designated focal points who act as representatives of the CNPV in corresponding PHPs. The choice of the focal points is based on the research topic. For example, researchers working on vaccine safety are designated as the focal point of the CNPV in the National Immunization Program. Much research related to drug and vaccine safety in the DRC have been organized as a result of this collaboration.19
There is currently an increased collaboration of the CNPV with the National Immunization Program with the support of the WHO. They are working together in order to implement a vaccine PV system following the National Immunization Program pathway. These activities will follow a model where the National Immunization Program will receive the funding to organize collection of adverse events following immunization in mass immunization and in routine immunization and will share the ICSRs with CNPV staff who will perform the data analysis as well as the signal detection activities. This collaboration is perceived as an opportunity for the CNPV to increase PV system coverage based on the National Immunization Program coverage, which is almost 100%.

**Bottlenecks.** There is still a poor coordination of safety surveillance of drugs used in PHPs. The CNPV has not yet been able to cover all the PHPs involved in the use of medicinal products in DRC. Not all PHPs are aware of the importance of PV and have included PV in their strategic or operational plans. For PHPs who have incorporate PV in their tools, there are different reporting tools, depending on funding, which overwhelm health care providers, making the reporting system less efficient.

**Collaboration with the National Regulatory Authority**

**Best practices.** Successful collaboration between the CNPV and the National Regulatory Authority has been built over the years. Understanding of the specificity of PV as well as the way it can contribute to the functions of the National Regulatory Authority was the main trigger of the implementation of the DRC PV center at the University of Kinshasa. Currently, the CNPV brings technical support to the National Regulatory Authority with regards to analysis of safety data and provision of evidence from the national database for decision making. Human resources from the CNPV are involved alongside the National Regulatory Authority in the analysis of evidence as well as in safety monitoring in clinical trials, the market authorization process, and post-marketing surveillance. The CNPV prepares monthly reports of the PV surveillance in post-marketing surveillance as well as for clinical trials. With the experience gained by CNPV staff over time, there is increasingly a clear demarcation between the responsibilities of the two institutions, which is favorable to better understanding and better collaboration. As a result of this increasing mutual collaboration, DRC is improving the quality of safety data analysis. In addition, the PV commission has started its activities and has initiated the first drug-related decisions based on international and national data, a committee for authorization and monitoring of clinical trials that is about to be implemented. Furthermore, collaboration with other institutions such as pharmaceutical companies and other international research institutions provided opportunities to the CNPV to improve its technical support to the national regulatory authority in order to shape the DRC PV system in light of international requirements, with an emphasis on clinical trials and post-marketing surveillance. As part of this collaboration, one member of CNPV staff was trained as a safety physician at GlaxoSmithKline (GSK) and another as PV oversight at MMV. They were both fellows granted by the Special Programme for Research and Training in Tropical Diseases (TDR) and The European and Developing Countries Clinical Trials Partnership (EDCTP). Currently, GSK is supporting DRC to improve its PV system as part of a project to enhance PV in sub-Saharan Africa.

**Bottlenecks.** There is a lack of comprehensive and validated guidelines for the activities of PV in DRC. PV regulation still seems not strong enough to attract collaboration by pharmaceutical companies and marketing authorization holders in safeguarding patient safety, which still leads to poor reporting about adverse events happening in the country by pharmaceutical companies. Despite the experience gained through several years of practice, stakeholders involved with the National Regulatory Authority are still insufficiently trained for analysis of regulatory dossiers related to clinical trials, market authorization delivery, and post-marketing decisions. There are still only a few CNPV staff with sufficient knowledge and expertise to contribute with technical support to the National Regulatory Authority, which limits the support that the CNPV can bring to the National Regulatory Authority. Finally, the fact that the regulatory activities in DRC are not well remunerated means stakeholders tend to focus more on other activities and leave regulatory matters as a lower-priority activity.
Main achievements

Implementation of PV at university

Installation of the DRC CNPV at the University of Kinshasa, in the Unit of Clinical Pharmacology and Pharmacovigilance has been one of the major realizations of the DRC PV system in a context where there is poor funding for PV systems and activities in developing countries. Universities offer an opportunity to have professionals committed to a new scientific area who are willing to collect data in order to perform research for their carrier development, which makes PV activities cost-effective. In this setting, the professionals have a basic salary for research and academic activities and are able to apply for additional grants and to interact with other universities or international research organization for capacity building. In addition, universities offer possibilities to recruit new staff based on topics that need to be addressed by the PV center. The status of academic staff allows more sustainable PV systems in African countries where instability of human resources in national institution is a concern. In Africa, there are several successful examples of national prosperous PV systems with PV centers based at universities such as in Morocco and South Africa.20,21

From data collection to signal detection

For several years, the main indicator of starting African PV systems was the number of ICSR collected and entered into the global database (VigiBase™) with poor attention on what should be done with these data. The main data analysis at this time was essentially related to individual case evaluation and causality assessment of ICSRs. The first short-course of signal detection provided by the UMC became available only in 2017.

In DRC, the ability of the University of Kinshasa staffs to perform analysis of the collected data in light of existing evidence was a good start point for further collaboration between the CNPV and the public health institutions. The ability of the CNPV to provide summary of safety data from the PV national database on PHP's request consolidated their relationship. The collaboration with the National Regulatory Authority improved when the CNPV became able to report statistics from the national database on a monthly basis, and to use its experience in drug safety in order to contribute to the analysis of evidence resulting from international or national data in order to inform decision making for marketing authorization and post-marketing surveillance. Signal detection activities starting in DRC threw new light on the way to collect data and for the necessity of extended data sources, which is an effective booster of the PV system. All these findings underline that PV systems based only on adverse events reporting will continue to perform poorly whereas a system based on data analysis to inform evidence is prone to be more prosperous.

The way forward

Although the collaboration with the national public health institutions improved with the sharing of evidence resulting from the analysis of international and national data, the involvement of health care providers improved with the feedback received in terms of acknowledge receipt, support for case management of serious adverse events, and pharmaceutical information exchange. Nevertheless, after a long work of implementation of PV culture in health care providers, commitment to PV activities decreased with the loss of touch with CNPV, mainly due to the withdrawal of funding in a context of a poorly accessible country. It is in that context that provincial PV centers are being implemented in DRC. The first assessment of these provincial PV centers showed a poor implementation of PV system in provinces mainly because of poor collaboration with provincial health authorities. This underlines one of the major weaknesses of the DRC PV system, which was based on the relationship between PV actors and health care providers who report adverse events directly to the CNPV, with poor involvement of health authorities from intermediate and operational level. The success of the DRC PV system in the future will rely on the ability of the CNPV to improve collaboration with health authorities at all levels in order to incorporate PV into the national health system. One of the solutions to solve the data collection issue is to explore the possibility of using the health information system as a channel for PV.22 In a context, where there is insufficient PV staff for the largest sub-Saharan African country and irregular funding, the existing and functional health information pathway constitutes a potential cost-effective way to collect data through the country. As it is anticipated that once data collection concerns are solved, CNPV staff will become overwhelmed with data entry
activities, it is mandatory to start building capacity in provincial health centers for data entry into VigiFlow® and to start thinking about how to implement best a sustainable electronic data entry system allowing all PV stakeholders to perform direct data entry in the system. In addition, in the medium term, the DRC PV system should also start thinking about patient reporting or at least improving the community-based PV system involving community health workers as an alternative to patient reporting in remote areas where access to health facilities is a challenge and higher illiteracy is expected.

Conclusions
Lessons learnt from the DRC experience show that it is possible to implement PV systems in resource-limited sub-Saharan African countries with no guaranteed funding. The ability of national PV centers to collaborate with public health stakeholders, including public health authorities at all levels as well as PHPs, and to use existing health information systems is the main key to success and may substantially reduce the cost of PV activities. PV systems will be prosperous in resource-limited sub-Saharan African countries if they will commit to addressing the need of all stakeholders and to addressing country-specific drug-related problems with the available resources and the capability to innovate based on country-specific realities. Scientific partnerships with pharmaceutical companies and research organizations is a huge opportunity to enhance the PV systems of resource-limited sub-Saharan African countries.

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