

## A Situational Analysis of Pharmacovigilance System in Republic of Benin

Aurel Constant Allabi<sup>1\*</sup> and Jude Nwokike<sup>2</sup>

<sup>1</sup>Unité de Pharmacologie, Faculté des Sciences de la Santé de Cotonou, Université d'Abomey-Calavi, Benin

<sup>2</sup>Management Sciences for Health, Strengthening Pharmaceutical Systems (SPS) Programs, Arlington, Virginia, USA

\*Corresponding author: Aurel Constant Allabi, MD, Ph.D., Unité de Pharmacologie, Faculté des Sciences de la Santé de Cotonou, Université d'Abomey-Calavi, 01 BP 188 Cotonou, Benin, Tel: +22996722151; E-mail: [acallabi@hotmail.com](mailto:acallabi@hotmail.com)

Received date: June 01, 2014, Accepted date: June 17, 2014, Published date: June 24, 2014

Copyright: © 2014 Allabi AC, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### ABSTRACT

**Background:** To date, no investigation has been carried out to systematically assess pharmacovigilance systems including quality control and resistance monitoring of artemisinin based combination therapies (ACTs) and other essential medicines in Benin.

**Objective:** To assess Benin's pharmacovigilance system, identify the gaps and define elements of strategy which could lead to successful establishment of a functional system in Benin.

**Methods:** Quantitative approach using structure questionnaires was applied to investigate physicians, pharmacists and pharmaceutical industry representatives' knowledge, attitude and practice regarding Adverse Drug Reactions (ADRs) reporting and the pharmacovigilance system in Benin. Specific questions examining the ADRs related to ACTs were also asked. Questions regarding reasons for non-reporting and important factors in a decision to report were also addressed.

The Indicator-based Pharmacovigilance Assessment Tool (IPAT) developed by the USAID-funded Strengthening Pharmaceutical Systems (SPS) program was also used to assess the current landscape with different stakeholders. Collecting data on the IPAT indicators was performed during different interviews of key informants. Reviewing documents from different stakeholders was done as well.

**Results:** All physicians and pharmacists have suspected at least one occurrence of ADR in their practice. 30.77% physicians and 31.11% pharmacists acknowledged that they faced at least one time ADRs suspected to be associated with antimalarial drug treatment (P-value<0.01). However none of the physicians or the pharmacists have ever reported ADRs to the national pharmacovigilance service. Significant difference (Chi2, P<0.05) was found between the proportion of physicians and pharmacists trained in pharmacovigilance (20% versus 1%). The main reasons for not reporting were "yellow card not available" and "not aware about the existence of pharmacovigilance center".

A small percentage (6.97%) of representatives of the pharmaceutical companies in the country monitors the safety of their products and none of them have ever reported ADRs to the health authority (DPM). In return, none of the laboratories have ever received a report related to quality or ADRs related to their drugs on the market from LNCQ or DMP.

Use of the IPAT tool led to these respective overall scores for core and supplementary indicators: 10 and 7 demonstrating that there is no functional pharmacovigilance system in place. Using these findings, a SWOT analysis was done. The major shortcoming is the lack of expertise in pharmacovigilance despite the availability of qualified human resource in the country. Several recommendations were also made with respect to critical immediate next steps to be taken to ensure that pharmacovigilance and medicine safety systems are developed and sustained in Benin.

**Conclusions:** This study has helped identify some of the critical challenges and barriers to promoting pharmacovigilance including control of quality and monitoring of ACTs resistance in Benin. There is a need to identify and implement adequate human resources use in order to build capacity and sustain the drug safety system for essential medicines and ACTs in particular. The Ministry of Health should involve all relevant stakeholders including the Faculty of Medicine and researchers to discuss these strategies and develop interventions for the successful implementation of pharmacovigilance in Benin.

**Keywords** Pharmacovigilance; Artemisinin-combinaison therapy; Control of quality; Benin

## Abbreviations

ADR: Adverse Drug Reaction; WHO: World Health Organisation; CNH-HKMU: Centre National Hospitalo-Universitaire Koutoukou-Maga; NPC: National Pharmacovigilance Center; NAFDAC: National Agency for Food and Drug Administration; IQR: Interquartile Range and Control; OTC: Over The Counter; PhV: Pharmacovigilance; ACTs: Artemisinin-based Combination Therapy; NPMIC: National Pharmacovigilance and Medicine Information Center; MoH: Ministry of Health; NGOs: Non Gouvernemental Organizations; IPAT: Indicator-based Pharmacovigilance Assessment Tool; NMCP: National Malaria Control Program (which is called PNLP in Benin); PNLP: Programme National de Lutte contre le Paludisme; LNCQ: Laboratoire National de Contrôle de qualité; DPM: Direction des Pharmacies et Médicaments; CMC: Comité Médical de Coordination; CRS: Catholic Relief Systems (NGO); AFRICARE: Africare (NGO); PISAF: Programme Intégré de Santé Familiale (NGO); ESS: Epidemiological Surveillance System; SNIGS: Système National d'Information et de Gestion Sanitaire; SOPs : Standard Operations Procedures; UMC: Uppsala Monitoring Center, the WHO Programme for International Drug Monitoring

## Introduction

ACTs are the current gold standard recommended treatment for uncomplicated malaria across the world [1]. They are extremely effective with cure rates higher than 95% in most studies. They are however expensive, and outside the reach of many people in Africa. However, with the establishment of the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund) in 2000, resources have been mobilized at the global level to ensure that all countries are able to access ACTs. In addition, other global health initiatives like the United States President's Malaria Initiative (PMI) and the Affordable Medicines Facility for Malaria (AMFm) are expected to lead to widespread deployment of ACTs in all endemic countries.

The widespread deployment of ACTs across Africa raises safety concerns in light of the absence of drug safety monitoring systems in the sub-region. The absence of safety experience with these products in West Africa means that policy makers and health workers are unaware of the actual safety and effectiveness of ACTs in West Africa as they relate to the genetic make-up of the population, the health systems and health care practices in the region and the impact of endemic diseases like onchocerciasis, schistosomiasis, HIV/AIDS and tuberculosis on the safety and effectiveness of ACTs. With increased access to essential medicines comes a greater need to monitor and promote the safety and effectiveness of these medicines. Few developing countries, however, have the structures, systems, or resources in place to support medicine safety activities, and countries often lack unbiased, evidence-based information to help guide treatment decisions and promote rational use of medicines [2].

Republic of Benin is one of such developing countries in Africa with high burden of malaria, and thus efforts to promote access to essential antimalarial medicines are on the increase. The change in malaria control policy in Benin in 2003 in favour of ACTs became necessary with the prevalence of *Plasmodium falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine[3,4].

Access to first line antimalarials ACTs in Benin is being driven by the AMFm program and the rescheduling from only being prescription medicines to over-the-counter medicines. They are now easily available and affordable at pharmacies, chemist shops,

dispensaries and health centers. Such informal use of antimalarials could increase the risk of incorrect dosing, inappropriate treatment and interactions of different medicines, which could have a negative impact on antimalarial treatment safety. Furthermore, there is a high demand for traditional medicines coupled with their uncontrolled advertisement through audio and print media which is also a point of safety concern.

Weak regulatory systems seen in most developing countries including Benin could lead to influx of unregistered brands of ACTs. Many studies have reported the huge impact that poor product quality, adverse drug reactions (ADRs), and medication errors have on health care in general and on patients' health in particular [5,6] but because most cases go undetected, estimating the current scale of this burden is almost impossible. The costs in lives and money may be higher in Benin because of the resource limitations of the health system infrastructure, unreliable supply and quality of medicines, and lack of adequately trained health care staff [7].

Pharmacovigilance 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' [8,9]. Pharmacovigilance has the potential to greatly reduce such preventable adverse events as occurs with the wider deployment of ACTs and contribute valuable evidence on which to base benefit-risk assessments. The success of a new treatment policy would depend on rational use, quality control and effective monitoring of the ACTs in terms of safety and effectiveness. A pharmacovigilance policy would also be required. Assessments that will provide data on ACTs' quality control, safety, and efficacy monitoring is therefore required. A current challenge with ACT safety gives us an opportunity to assess status of global pharmacovigilance system and diagnose its strengths, weaknesses, and gaps.

In order to comprehend the issues presented in this article, it is important to understand the structure of the regulatory authorities in Benin, including the pharmacovigilance system. DPM is a technical division of the MoH. It is the steering structure in charge of regulatory activities related to drugs and pharmaceutical services in the country. In spite of the fact that LNCQ is under administrative control of DPM, LNCQ is autonomous organ at MoH and is in charge of controlling the quality of all drugs and reagents in the country. PNLP is a national malaria control program and its objective is to bring down malaria burden in the country. CNHU is the biggest hospital of the country. It is a teaching hospital and has also the status of technical direction of MoH.

This article seeks to draw up a portrait of policy documents and practical actions in the areas of pharmacovigilance, quality control of ACTs and monitoring of resistance of ACTs in Republic of Benin (situational analysis), identification of the main barriers which prevent their implementation and the discussion focus on the recommendations for towards the establishment of an effective and functional of a pharmacovigilance system in Benin.

## Methodology

### Study procedure

The assessment was conducted for a period of two weeks in May 2009, in Benin. Surveys were conducted in order to assess the knowledge attitude and practice of different stakeholders of the health system involving pharmacovigilance, quality control and monitoring

of ACT resistance. Data sources were identified, gathered and analyzed including documents related to the regulation of pharmacovigilance, quality control and monitoring of ACTs resistance.

Interviews were carried out on two groups of respondents, the first group included physicians, pharmacists and representatives of pharmaceutical companies.

**Quantitative approach:** A Quantitative approach with a semi-structured questionnaire was used to investigate physicians, pharmacists and representatives of pharmaceutical companies' attitudes. For the first group, a sample of 156 interviewees including 68 physicians, 45 Pharmacists and 43 representing of pharmaceutical companies, all practicing in Cotonou were selected. Sampling of physicians was done based on systematic random sampling from regional list of physicians practicing in Cotonou furnished by the "Ordre National des Médecins du Bénin". Interviews of pharmacists were done based on systematic random sampling from regional list of pharmacists practicing in Cotonou furnished by the "Ordre National des Pharmaciens du Bénin". Interviews with representatives of pharmaceutical companies were done based on systematic random sampling from regional list furnished by the association of representative of pharmaceutical industries.

In person interviews were conducted with physicians, pharmacists, and representative of pharmaceutical companies. A questionnaire based on ADR reporting, reasons for non-reporting was used to investigate knowledge, attitude and practice of these actors. Specific issues were addressed examining the ADRs related to ACTs.

The second group included stakeholders, namely institutions based at the Ministry of Health: National laboratory of drugs control quality (LNCQ), Direction of Pharmacies and drug regulations (DPM), National Malaria Control program and the Director of the teaching hospital in Cotonou (CNHU).

**Qualitative approach:** Qualitative approach was used when interviewing the second group. We chose a qualitative research because this methodological approach could identify these regulatory authorities' point of view and would facilitate the development of ideas for possible interventions. The qualitative technique used was the focus group methodology [10]. The focus groups consisted of representatives from PNLP (NMCP), LNCQ, DPM and the director of the CNHU-teaching hospital. All stakeholders who were contacted agreed to participate in the study.

Sessions organized with each stakeholder of this second group were relaxed and lasted between 1 and 2 h. Each focus group session consisted of a short introduction, undertaken by a principal investigator, describing the objectives of this study. Then, participants were requested to answer specific questions included in the questionnaire and discuss problems in the pharmacovigilance system and control of quality of ACTs according to their particular point of view and ways to solve these problems.

Participants were informed that the purpose of the study was to assess the practice, understand their perception of the problems and ways to improve it. Open-ended questions were used to generate discussion in both areas: problems and possible solutions. Notes on the themes that emerged from the discussion were reviewed with participants on the second or third visit to clarify statements and to ensure the transcripts were complete. For each session, content analysis using an open analytic approach was employed to explore and understand the practice and problems of the stakeholder.

This method uses no predetermined categories of analysis and allows incorporation of relevant themes and issues that emerge from the data to guide the coding and facilitate a more detailed understanding of the context and processes related to the problem. An inductive and iterative analytical process was used to seek out all relevant interpretations and that was continued until no new information emerges.

### **IPAT tool**

Additionally, the authors used SPS's recently developed Indicator-based Pharmacovigilance Assessment Tool (IPAT) [11-13]. It is a diagnostic tool for the assessment of pharmacovigilance systems in developing countries such as Benin. The IPAT is used to support evidence-based options analysis and development of relevant and feasible recommendations reflecting local realities, existing regulatory capacity and priorities, identified system gaps, and available resources. The assessment involved document reviews, structure questions, and key informants interviews. The structured part of the assessment includes 25 core indicators and 17 supplementary indicators. The assessment focus on drug regulation system (DPM), National malaria control program (PNLP), Control quality of drugs center (LNCQ) and the biggest teaching hospital (CNHU).

Using finding from the analysis we conducted a SWOT analysis to identify strengths, weaknesses, opportunities and threats and used that to build recommendations that were presented.

## **Results**

### **Knowledge, attitudes, perceptions and expectations of pharmacists, physicians to adverse drug reaction reporting in Benin**

Sixty-eight physicians, 45 pharmacists and 43 representatives of pharmaceutical companies were interviewed using semi-structured questionnaire. It was found that all physicians and pharmacists had suspected at least one time ADR in their practice. For antimalarial drugs, specifically, 30.77% physicians versus 31.11% pharmacists acknowledged that they faced at least one ADR in their practice that is likely associated with ACT use. No Physicians or pharmacists (0.0%) had ever reported ADRs to pharmacovigilance service. However, 50.77 % of physicians and 48.89% of pharmacists reported that they had verbally communicated about these cases with other structures or health practitioners.

Significant difference was found between the proportion of physicians and pharmacists trained in pharmacovigilance (20% versus 1%). At the time of this survey, pharmacists who are major health care professionals in the private sector have not undergone training on pharmacovigilance. No ADR reporting forms were available neither at the workplaces of physicians nor pharmacists. The main reasons for not reporting were "yellow card not available", "not aware about the existence of pharmacovigilance center", "not aware about the existence of pharmacovigilance system", and "lack of knowledge of how to access ADR forms" (Table 1).

### **Knowledge, attitudes and practices of representatives or delegates of the pharmaceutical companies**

A small proportion (6.97%) of representatives of the pharmaceutical companies monitor at regular basis the ADRs of the medicines they

hold authorization for marketing. All the pharmaceutical manufacturers assessed indicated that reports were sent to their headquarters but not to the ministry of health in Benin. 39 out of those 43 surveyed indicated that they have own internal pharmacovigilance

system. No ADR reporting was sent to the DPM by the representatives of the pharmaceutical companies and none of the pharmaceutical companies have experienced the withdrawal of their product from market.

Knowledge, Attitudes and Practices of Interviewees	Physicians		Pharmacists		P-value
	Yes	No	Yes	No	
Have the patients reported you ADRs ?	96.92	3.08	100.00	0.00	
Have you experienced any case of ADRs where antimalarial was suspected?	30.77	69.23	31.11	68.89	<0.01
Do you report ADRs to National Pharmacovigilance center?	3.08	96.92	2.22	97.78	0.74
Do you report ADRs to another center?	50.77	49.23	48.89	51.11	0.04
Have you been trained on the spontaneous reporting and pharmacovigilance system in the country?	20.00	80.00	15.56	77.78	0.35
Are ADRs reporting form available in your office?	0.00	100.00	0.00	100.00	

**Table 1:** Knowledge, Attitude and Practice of Health Professionals (Physicians and Pharmacists) about spontaneous reporting of adverse drug reactions (ADRs).

No pharmaceutical companies have ever received reports related to the quality of their drugs already on the market from LNCQ or DMP.

### Assessment of pharmacovigilance and control of quality of ACTs practices at the regulatory level (DPM, LNCQ, CNHU)

**Interviews with the Leaders of the DPM:** Throughout several sessions, this focus group reviewed various relevant documents including policies, laws, standard operating procedures and working instructions documents, and discussed them. In Benin, there is one office dedicated to pharmacovigilance called Pharmaceutical Inspection and Pharmacovigilance Service. Only one person worked in this service. Neither the SIPP nor the DPM were adequately staffed (in terms of manpower and skill sets) to take on full responsibility for pharmacovigilance and other regulatory activities.

**Available Policies, Laws and documents:** The Benin National Drug Policy recognizes the need for pharmacovigilance and medicine information services and considers post-marketing surveillance and pharmacovigilance important aspects of medicines registration and selection in Benin. The following pharmacovigilance legal documents are available:

- Order No. 1801/MS/DC/SGM/CTJ/DPM/SA of February 20, 2007, which defines functions, organization and functioning of the direction of pharmacies and medicines of Benin. Article 11 defines the tasks of the Pharmaceutical Inspection and Pharmacovigilance Service.
- Order No. 4182/MSP/DC/DPHL/SPM, which defines duties and functions of the Technical Committee on Drugs.
- ADR form: There is as of yet no document defining the National Policy on Pharmacovigilance which would enable the enforcement of PhV activities. It was learnt that this document was currently under development.

**Interviews with NMCP:** At the level of NMCP (PNLP), the following documents were found: Procedures manual for ADR

reporting where ACTs were suspected, manual of Protocol developed to monitor antimalarial drug (ACT) efficacy including their resistance.

Several references concerning the management of malaria and national policy for the control of malaria were also found. Monitoring of ACTs efficacy and safety is clearly defined by NMCP. However, it lacks the legal provisions to enforce those activities.

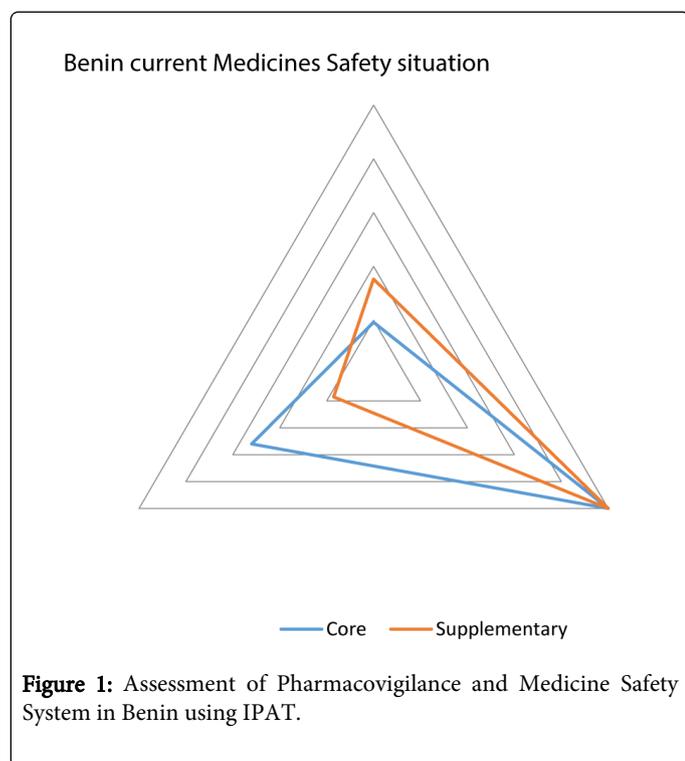
**Interview with LNCQ Leaders:** LNCQ perform control of quality of antimalarial drugs and specifically ACTs, but only prior to being released on the market. There is no set schedule for quality control of antimalarial drugs or ACTs in particular. Quality control of antimalarial drugs has not taken place regularly due to events or circumstances; the usual sites of sampling for quality control are: health centers, area hospitals, pharmacies, the NMCP, drug donations. Relations with the NMCP and PhV service are mostly limited to quality control of antimalarial drugs. There are no developed plan involving cooperation with NMCP and DPM.

In Benin, where the quality of products can be variable [7](ASS, 2008), reliable testing of ACTs is not always affordable due to diverse reasons: lack of solvents, control products, internal standards, or financial resources. One proposal to improve this aspect of pharmacovigilance of ACTs is to ensure that there is systematic testing prior to importation and before the availability of ACTs in the distribution chain. The MoH and health authorities should ensure that antimalarial medicines including the ACTs in circulation are of good quality and that patients understand how the products should be taken.

**Interview with the leaders of hospitals:** Three different sessions were held with the Director of CNHU. The key take aways from these discussions were: There is no committee to monitor ADRs in the hospital. PhV activities are, for now, lacking at the CNHU. There is no structure within the CNHU with this prerogative. There are no formal relationships between the NMCP and CNHU or pharmacovigilance system. Spontaneous adverse event reporting is not yet available to the CNHU. However, officials have met with the DPM CNHU authorities

to set up a pharmacovigilance structure and wishes to also meet and discuss opportunities for strengthening PV with the CMC. The Director of CNHU showed high interest for PhV and hoped that the center collaborate with the CNPV whom he considers to be an essential structure of health protection for the entire country.

**Systems, structures, and stakeholder coordination:** Using the indicator-based pharmacovigilance assessment tool (IPAT), data was collected at the MoH (DPM), NMCP (PNLP), LNCQ and at the biggest teaching hospital (CNHU), and the findings are presented in Figure 1. Each “Yes” on a core indicator is given a score of 2; each supplementary indicator that is achieved is given a score of 1, resulting in a total possible score of 52 for the core indicators and 17 for the supplementary indicators. This presentation allows visual recognition of gaps and improvements over time. Table 2 and Figure 1 show clearly that there is no national pharmacovigilance coordinating center. There is no functional information and technology infrastructure, including a lack of ADR forms for health professionals to report incidents.



Benin has been an associate member of the WHO Collaborating Center for International Drug Monitoring for many years but has not been able to progress to full membership of the monitoring program because of the stagnation of pharmacovigilance development in the country.

Findings using IPAT is shown in Figure 1.

### Findings-Strengths

The following documents exist:

- National Pharmaceutical Policy (PhV-related policy being part)
- Guidelines for ACT efficacy monitoring (PNLP)
- ADR form
- In-service training curriculum on PhV initiated by NMCP

- PhV topics include in the medicine and pharmacy curriculums
- Active surveillance studies initiated in public health programs (PNLP and other public health programs: TBC, HIV/AIDS etc.)

### Findings-Current Constraints (Table 2)

Constraints	Impact
PhV policy not finalized	Addressing medicine safety is not viewed as obligatory
No Food and Drug Act-No guidelines for Medicines Safety Surveillance in Benin	Marketing Authorized Holders not required to report ADRs neither submit periodic safety update reports; Enforcement not possible
No PhV center, no guidelines, notification system not yet approved-PhV unit is currently merged with Pharmaceutical Inspection unit without clear guidelines	PhV activities cannot be formally operationalized
No existence of National PhV working committee	PhV agenda could not move
No Drug Therapeutic Committees in major hospitals e.g National teaching hospital	Essential structure for drug safety monitoring at the health facility level is lacking
Insufficient in-service and pre-service training	HCP have limited skills to monitor adverse events
No formal mechanism of medicine safety information services	HCP and patients are not well informed
No organized system to improve or monitor patient safety relating to medicine use	Opportunities to use adverse events incidences to prevent future occurrences are lost
Isolated and uncoordinated PhV activities	Inefficient use of resources
PHPs do not consistently track and consolidate ADR & treatment failure data	No data to inform treatment guidelines decision
Absence of regular drug quality control at different level of supply chain	Patients may lose confidence in the health delivery system

**Table 2:** Findings-Current Constraints.

### Findings-Opportunities

- NMCP (PNLP), Pharmacology unit at Faculty of Medicine and other stakeholders highly committed to the issue of PhV in Benin.
- PhV-related trainings exist already and majority of Health professionals admit to extend and repeat those trainings.
- Various trainings led by NMCP and Faculty of Medicine in the frame of management of severe malaria were also provided to health professionals.
- Donor communities are sensitized and supportive to the need for PhV system.

Besides the MoH, other bodies such as the Global Fund, USAID, and WHO are leveraging funding for PhV, Sentinel sites were identified for the purpose to follow efficacy and resistance of ACTs. One previous efficacy study was already done but the data were not published. The findings of this study may be important in understanding the efficacy and the resistance profile of ACTs in Benin.

Several pharmacovigilance studies were initiated by the Pharmacology unit of Faculty of Medicine and are currently ongoing (Safety of ACTs in Cotonou, Benin-Cohort Study; Safety of medicinal plants in Agonlin area). A project of creating a University Hospital Center of Pharmacovigilance, Drug, and Poison of Information on Medicines is pending, waiting for resources to be implemented.

Pharmacovigilance has gradually been gaining attention and interest, as among NGOs and other organizations. Africare and Catholic Relief Services (CRS) have included in their action plans a number of activities to strengthen the system of pharmacovigilance such as the reproduction of data collection tools at rural community level and the establishment of a recovery system of data from communities to the national health system.

## Discussions and Recommendations

According to our knowledge, this study is the first to explore the scope of pharmacovigilance including quality control and monitoring of resistance of ACTs in Benin and Africa with the aim to perform situational analysis involving all stakeholders and majority of perspectives related to the control of ACTs safety.

Pharmacovigilance has gained wide global interest since the 1990s as illustrated by the number of reports in the WHO global individual case safety report (ICSR) database as well as the number of countries joining the WHO Pharmacovigilance programme [14]. Despite this global progress, the situation in Benin is still alarming. A national pharmacovigilance reporting system is non-existent, as is the case in other sub-Saharan African countries. This is illustrated by the fact that only 60 individual case safety reports (ICSRs) suspecting ACT have ever been submitted by nine countries (four of them located in Sub-Saharan Africa) from 2001 to 2008, even though ACT is nowadays widely distributed in endemic countries [15]. Those reports were all sent to UMC after the WHO recommendation to use ACT for uncomplicated malaria was published in 2001 [16]. Similar results about health professionals experience related to ADRs (92.4% vs 100% in our study) were found in Nigeria [17]. The percentage of those who report in their study were higher compare to what it is seen in Benin (25.5% vs 0%). This significant difference is due to the existence of supra-structure and highly visible National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria. Main reasons for not reporting in our study were: unaware of existence and availability of the yellow card reporting for ADR, not knowing about the existence of pharmacovigilance center, lack of awareness of pharmacovigilance systems. Similar reasons were found in previous studies from different countries [18,19].

Identification of the main barriers and weakness will help in the development of recommendations for the establishment of effective and functional pharmacovigilance system in the country.

### Establishment of an operational and effective Pharmacovigilance system and role of the University

The visibility of PhV at Ministry of Health should be increased by establishing an independent National Pharmacovigilance and Medicine Information Center (NPMIC) to focus on addressing all issues related to monitoring of the safety, effectiveness, promotion and advertising of health products post-authorization. The scopes of activities for this proposed unit are very extensive and critical to appropriate use of medicines in Benin. A unit for addressing pharmacovigilance and medicines information can complement most

of the current activities of the regulatory system. From our study it was apparent that other units of the MoH that would have included the PhV activities in their mandate are currently overstretched and lacking the necessary human resources and skills to adequately fulfill this function [7]. The establishment of a NPMIC with well-defined organization chart will be a key to success. Autonomous status with a specific mandate would allow the center the capacity to succeed by increasing its visibility. In addition, the formalization of a technical committee of pharmacovigilance (Figure 2) will help to define agenda and enable related activities.

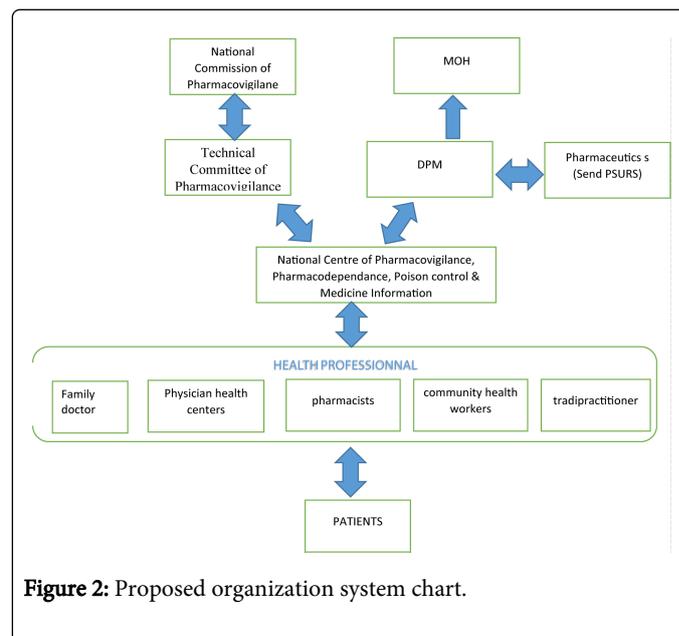


Figure 2: Proposed organization system chart.

In general, pharmacovigilance is a multidisciplinary issue that involves disciplines such as clinical pharmacology, clinical medicine, toxicology, epidemiology and genetics [20]. Unfortunately, human resources with these expertises are few in Benin and thus it is imperative to use these scarce resources wisely. A NPMIC team overseeing pharmacovigilance activities in the country should be headed by a Pharmacovigilance expert who will aid the team to produce the highest-quality safety data. A qualified person for pharmacovigilance (QPPV) should be identified also at the regulatory side such as MoH.

It is desirable to ensure a strong link between the NPMIC and the Faculty of medicine as the pharmacology unit to provide PhV training to pharmacy and medicine students. This would be mutually beneficial; as a consequence, students could help carry out the permanent activities of the NPMIC. Developed countries such as France use this strategy to have students in regional pharmacovigilance centers, which give them the opportunity to learn by doing. NPMIC should collaborate extensively with clinicians from different specialties and with academia and drug research units. A multi-disciplinary technical committee to assist NPMIC on technical matters is recommended. Given all the arguments developed above, it is more feasible and efficient to implement NPMIC at the biggest teaching hospital or at the faculty of health sciences. The clinical pharmacology unit of the faculty of medicine could mobilize the technical expansion of pharmacovigilance in the country. Previous successful examples can be seen in South Africa, Zambia, and Morocco. The National Adverse Drug Events Monitoring Center

(NADEMEC) is located within the University of Cape Town. There is also an HIV/AIDS Adverse Drug Events Unit within the University of South Africa at Pretoria, and an Adverse Drug Reaction in Pregnancy and Neonates Unit at the University of Bloemfontein. Both of these units receive initial reports, and then forward them to NADEMC, which has served as a training location for pharmacovigilance initiatives in Africa. This lesson is not only relevant for Benin but for all developing countries seeking to improve their pharmacovigilance systems.

There should also be the implementation of active pharmacovigilance studies. A prospective cohort study tracking patients on ACTs, Active surveillance in sentinel sites among target groups such as pregnant women and children under 5 years would provide an overview of drug safety in the country.

An elaboration of pharmacovigilance system is an essential step. Various health systems that are already established in the country, such as SNIGS or epidemiological surveillance system (ESS) could be the basis of a pharmacovigilance system with some adaptations (Figure 3). Through our analysis, it appears that the ESS is the most compatible with pharmacovigilance activities. A PhV system based on this existing EES with some adaptations could be implemented and evaluated after one year. The proposed system is shown in Figure 2.

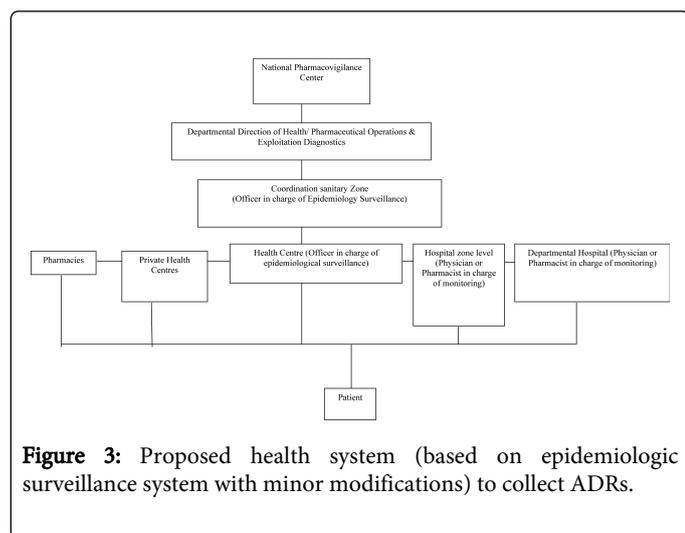


Figure 3: Proposed health system (based on epidemiologic surveillance system with minor modifications) to collect ADRs.

It is advisable to fill the gaps related to policy and regulatory provisions. Law and decrees organizing the Pharmacovigilance system in Benin should be adopted and implemented contributing to the strength of the system. Risk mitigation systems, protocols and SOPs should also put in place to emphasize medicines safety at every stage.

### Education and Training of Health Professionals on Pharmacovigilance and ADRs reporting

Health professionals in both public and private sector (doctors, pharmacists, nurses, midwives, laboratory technicians, responsible for disease surveillance, etc.) in Benin should receive training on how to recognize ADRs and to report them. In addition, health workers and community health workers (CHW) should be trained on ADRs reporting due to their prominent role in caring for uncomplicated malaria. NGOs such as CRS, Africare and PISAF have already shown their interest to achieve this goal (Personal communication).

At the time of this survey, pharmacists who are major health care providers in the private sector have not undergone training on PhV. Among those who have already undergone training in PhV the objective will be to maintain a high rate of reporting ADRs. Local strategies to stimulate reporting on ADRs should be developed and implemented.

### Quality control and Monitoring of ACTs resistance

The rapid increase of antimicrobial-resistant strains for established and new-generations of drugs make drug resistance a global problem. This is a broader and more critical threat in African countries because in addition to antibiotics, the continent's disease burden is heavily biased toward three infectious diseases particularly susceptible to the rapid development of resistance: HIV/AIDS, malaria, and tuberculosis [21].

In order to properly monitor resistance, activities related to prevalence determination of molecular markers of ACTs resistance should be implemented to evaluate regularly the efficacy of ACTs. Monitoring ACT resistance should be conducted at sentinel sites, selected in such a way as to have a variable rate of self-medication, the penetration rate of ACTs and therapeutic arsenal. Information obtained through such studies could be used to direct scientific analyses of reported adverse events and reactions. Early warning signals of the development of drug resistance could be generated from spontaneous database reporting.

In general, promotion of rational use of ACTs will succeed only if rational use of all drugs authorized in the country is addressed. The national therapeutic guide or compendium, flowcharts for therapeutic management development and its dissemination to physicians and health professionals must be a part of this global process.

Establishment of Drug Therapeutic Committees (DTC) in all public and private health facilities could also increase the rational use of medicines. Bringing together diverse expertise this committee should develop and implement a drug policy adapted to the context of hospital. Scope of activities of the Committee could include monitoring of safety and treatment failure, streamlining of prescription drugs outside form of intervention in various procedures, introduction of new treatment protocols, drug quantification process, support active surveillance, failure in the chain of permanent pharmaceuticals assessment system (recommendation WHO).

### Conclusion

With globalization and the rapid introduction of high-tech medicines into the distribution chain, the issue of the quality, efficacy and safety of medicines is becoming of great concern for many developing countries such as Benin with uncontrolled pharmaceutical and health service delivery sectors. The country recognizes the need to set up system to monitor the safety of newly introduced medicines, such as ACTs. Despite this enthusiasm, only limited progress has been made. To achieve this goal, a well-organized drug agency and PhV system needs to be developed. The rational use of human resources available in the country is needed to achieve this objective. Sub-Saharan African MoHs will gain a lot by recognizing and utilizing available opportunities including human resources at university for example to build an efficient system. Failure to enforce regulations would result in the proliferation of harmful, inefficacious, counterfeit or substandard medicines on national and international markets. This assessment has provided a baseline on the status of pharmacovigilance

activities in Benin. The recommendations provided, when implemented, will initiate efforts at improving the system and monitoring progress over time.

## References

1. McIntosh HM, Olliaro P (2000) Artemisinin derivatives for treating uncomplicated malaria. *Cochrane Database Syst Rev* : CD000256.
2. Strengthening Pharmaceutical Systems (2009) Supporting Pharmacovigilance in Developing Countries: The Systems Perspective. Management Sciences for Health.
3. Falade CO, Salako LA, Sowunmi A, Oduola AM, Larcier P (1997) Comparative efficacy of halofantrine, chloroquine and sulfadoxine-pyrimethamine for treatment of acute uncomplicated falciparum malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 91: 58-62.
4. Aubouy A, Fievet N, Bertin G, Sagbo JC, Kossou H, et al. (2007) Dramatically decreased therapeutic efficacy of chloroquine and sulfadoxine-pyrimethamine, but not mefloquine, in southern Benin. *Trop Med Int Health* 12: 886-894.
5. Pirmohamed M, Atuah KN, Dodoo AN, Winstanley P (2007) Pharmacovigilance in developing countries. *BMJ* 335: 462.
6. Talisuna AO, Staedke SG, D'Alessandro U (2006) Pharmacovigilance of antimalarial treatment in Africa: is it possible? *Malar J* 5: 50.
7. *Annuaire des Statistiques Sanitaires* (2008) Ministère de la Santé-République du Benin.
8. Edwards IR, Biriell C (1994) Harmonisation in pharmacovigilance. *Drug Saf* 10: 93-102.
9. World Health Organization (2002) The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products. World Health Organization.
10. Mays N, Pope C (1995) Rigour and qualitative research. *BMJ* 311: 109-112.
11. Kitzinger J (1995) Qualitative research. Introducing focus groups. *BMJ* 311: 299-302.
12. Strengthening Pharmaceutical Systems (2009) Indicator-Based Pharmacovigilance Assessment Tool: Manual for Conducting Assessments in Developing Countries. Management Sciences for Health.
13. Nwokike J, Joshi M (2009) Assessment of Pharmacovigilance and Medicine Safety System in Rwanda. U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program, Arlington, VA: Management Sciences for Health.
14. Olsson S, Pal SN, Stergachis A, Couper M (2010) Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. *Drug Saf* 33: 689-703.
15. Kuemmerle A, Dodoo AN, Olsson S, Van Erps J, Burri C, et al. (2011) Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin-based combination therapy, to the WHO Programme for International Drug Monitoring. *Malar J* 10: 57.
16. Roll Back Malaria (2001) Antimalarial Drug Combination Therapy: Report of a WHO Technical Consultation. World Health Organization, Geneva.
17. Ohaju-Obodo JO, Iribhogbe OI (2010) Extent of pharmacovigilance among resident doctors in Edo and Lagos states of Nigeria. *Pharmacoepidemiol Drug Saf* 19: 191-195.
18. Toklu HZ, Uysal MK (2008) The knowledge and attitude of the Turkish community pharmacists toward pharmacovigilance in the Kadikoy district of Istanbul. *Pharm World Sci* 30: 556-562.
19. Hazell L, Shakir SA (2006) Under-reporting of adverse drug reactions : a systematic review. *Drug Saf* 29: 385-396.
20. Oshikoya KA (2010) Adverse event monitoring of artemisinin combination therapy in Nigeria: the challenges and limitations of the study. *West Afr J Med* 29: 221-224.
21. Huff-Rousselle M, Simooya O, Kabwe V, Hollander I, Handema R, et al. (2007) Pharmacovigilance and new essential drugs in Africa: Zambia draws lessons from its own experiences and beyond. *Glob Public Health* 2: 184-203.