ANALYSE DE LA SITUATION DE LA PHARMACOVIGILANCE AU BENIN: EXEMPLE DES COMBINAISONS THERAPEUTIQUES A BASE D'ARTEMISININE (CTAS)

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RESUME

Aucune investigation systématique n'est menée pour évaluer la pharmacovigilance y compris le contrôle de qualité, le monitoring de l'efficacité et la détection de la résistance aux CTAs, au Bénin.

Objectif :

Evaluer la pharmacovigilance des CTAs y compris le contrôle de qualité, la détection des résistances aux CTAs,

Identifier les insuffisances et proposer des stratégies pouvant rendre fonctionnel le système national de PV.

Matériels et Méthodes :

Une approche quantitative est mise en œuvre grâce à des questionnaires structurés administrés aux médecins, pharmaciens et représentants des industries pharmaceutiques en vue d'appréhender leur connaissance en un premier temps des attitudes et pratiques eu égard à la notification des effets indésirables et en un second temps du système de pharmacovigilance au Bénin. Des questions spécifiques relatives aux effets indésirables associés aux CTAs et les raisons de la non-notification sont aussi posées.

Une approche qualitative et l'outil IPAT sont utilisés pour évaluer la situation actuelle avec les différents acteurs réglementaires. La collecte des données relatives aux différents indicateurs a été réalisée pendant les différentes interviews des informateurs clés. La revue des documents a été aussi effectuée.

Résultats :

La totalité (100%) des médecins et pharmaciens interrogés ont expérimenté au moins une fois un cas d'évènement indésirable dans leur pratique. 30.77% des médecins contre 31.11% des pharmaciens ont identifié au moins une fois un effet indésirable associé à un antipaludique (P-value<0.01). Cependant, aussi bien les médecins que les pharmaciens n'ont jamais notifié un cas d'effet indésirable au service national de pharmacovigilance. Il existe une différence significative entre les proportions de médecins et pharmaciens ayant suivi une formation en pharmacovigilance (20% versus 1%). Les principales raisons de la non-notification sont « fiches de notification non disponibles », « n'être pas informé de l'existence d'un service national de pharmacovigilance ».

Une faible proportion (6.97 %) des représentants des industries pharmaceutiques développent des activités de suivi de la sécurité de leurs produits et aucun d'entre eux n'a jamais rapporté un évènement indésirable associé à leurs produits aux autorités de santé (DPM). En retour, aucun des laboratoires n'a jamais reçu une alerte provenant du LNCQ ou de la DPM relative à la qualité ou aux évènements indésirables associés à leurs produits sur le marché.

En utilisant l'outil IPAT, les indicateurs de base et complémentaires sont estimés respectivement à 10/52 et 6/17 indiquant qu'il n'existe pas de système fonctionnel de pharmacovigilance en place au Bénin. Une analyse FFMO a été faite. L'insuffisance majeure est le manque d'expertise malgré la disponibilité de ressources humaines qualifiées au niveau du pays. Plusieurs recommandations sont faites pour assurer l'implémentation, le développement et le maintien du système de pharmacovigilance au Bénin.

Conclusion : Cette étude a permis d'identifier les barrières et défis empêchant la promotion de la pharmacovigilance au Bénin. Il est essentiel d'identifier les ressources humaines et de les utiliser de façon rationnelle afin de renforcer les capacités et soutenir le système global de pharmacovigilance et celui des CTAs en particulier. Informé et sensibilisé sur ce retard, le Ministère de la Santé doit utiliser

la Faculté de médecine comme un levier dans l'implémentation de la pharmacovigilance dans tout le pays.
Mots clés: Pharmacovigilance, Combinaison Thérapeutique à base d'Artémisinine, Contôle de qualité, Bénin

ABSTRACT
Background: No investigation was carried out a systematic assessment of pharmacovigilance including quality control and resistance monitoring of artemisinin based combination therapies (ACTs).
Objective: To assess this situation, identify the gaps and define elements of strategy which could lead to successful establishment of a functional pharmacovigilance system in Benin.
Methods:
Quantitative approach using structure questionnaires was applied to investigate physicians, pharmacists and representatives of pharmaceutical industries knowledge, attitude and practice regarding Adverse Drug Reactions (ADRs) reporting and pharmacovigilance system in Benin. Specific questions examining the ADRs related to ACTs were also asked to them. Questions regarding reasons for non-reporting and important factors in a decision to report were also addressed.
Qualitative approach and Indicator-based Pharmaceutical Assessment Tool (SPS) were used to assess the current landscape with different stakeholders. Collecting data on the indicators was performed during different interviews of key informants described above. Reviewing documents from different stakeholders was done as well.
Results:
All physicians (100%) and pharmacists (100%) have already suspected at least one time the occurrence of ADR in their practice. 30.77% physicians versus 31.11% pharmacists faced at least one time ADRs where antimalarial drugs were suspected (P-value<0.01). However Physicians as well as pharmacists (0.0%) have never reported ADRs to the national pharmacovigilance service. Significant difference 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'', "not aware about the existence of pharmacovigilance center".
Minor proportions (6.97 %) of representatives of the pharmaceutical companies in the country monitor the safety of their products and none of them have ever reported ADRs to health authority (DPM). In return, all laboratories have never received report related to the quality or ADRs related to their drugs on the market from LNCQ or DMP.
Findings using IPAT tool, lead to these respective overall scores for core and supplementary indicators: 10 and 6 explaining that there are no functional pharmacoviglance system in place. Using findings, a SWOT analysis was done. The major shortcoming is the lack of expertise despite 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 special challenges and barriers to promoting pharmacovigilance including control of quality and monitoring of ACTs resistance in Benin. It needs to identify and implement adequate human resources use in order to build capacity and sustain the safety system globally and ACTs in particular. Learning from its failure, Ministry of Health should definitely use University or Faculty of Medicine as a pathfinder for successful pharmacovigilance implementation in the country**.**
Key-words: Pharmacovigilance, Artemisinin-combinaison therapy, control of quality, Benin

INTRODUCTION

Artemisinin-based combination therapies (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 against 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, newer 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 view of the absence of drug safety monitoring systems in the sub-region. The absence of safety experience of these products in West Africa means that policy makers and health workers are unaware of the real life safety of ACTs in West Africa as it relates to the genetic make-up of the population, the health systems and heal-

thcare practices in the region and the impact of endemic diseases like onchocerchiasis, 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.

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 artemisinin-based combination therapy (ACT) became necessary with the prevalence of *Plasmodium falciparum* resistance to chloroquine and sulphadoxine-pyrimethamine (Falade CO et al, 1997; Aubouy A et al, 2007).

Access to first line antimalarials ACTs in Benin, is being driven by the AMFm program and this has caused its shift from only being prescription medicines to over-the-counter medicines. They are now easily available and affordable at pharmacies, chemist shops, dispensaries and health centres. 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 on the audio and print media which is also a point of safety concern.

However, increased access 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 (Pirmohammed M *et al*, 2007; Talisuna AO *et al*, 2006), but because most cases go undetected, estimating the current scale of this burden is almost impossible. The costs in lives and money are much worse because of the poorer state in Benin, of health system infrastructure, unreliable supply and quality of medicines, and lack of adequately trained health care staff (Annuaire des Statistiques Sanitaires, 2008, Ministère de la Santé du Bénin).

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' (Edwards and Biriell 1994, World Health Organization 2002). Pharmacovigilance has the potential, to greatly reduce such preventable adverse events 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 efficacy. A binding pharmacovigilance policy would also be required. This assessment is therefore timely and would provide data on ACTs quality control, safety and efficacy monitoring. A current challenge with ACT safety gives us an opportunity to assess status of global pharmacovigilance system and diagnose its strengths, weaknesses, and gaps.

This article seeks also 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

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

During this assessment, we identified, gathered and analyzed data sources including documents related to the regulation of pharmacovigilance, quality control and monitoring of ACTs resistance.
Interviews were carried out on the two groups, after the topic was introduced to the participants.

The first group included Physicians, Pharmacists and Representative of pharmaceutical companies.
Quantitative approach with a structured questionnaire was used to investigate physi-

cians, 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 Benin".

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.

Face-to Face 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 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 [7bis, 8bis]. The focus groups consisted **PNLP (NMCP), LNCQ, DPM and Director of 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 audit 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. We took notes on themes emerging from the discussion and also compared notes on second or third visit. This was done in order 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 Pharmaceutical Assessment Tool (IPAT) (SPS 2009; Nwokike J. and Joshi M. 2009). 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 centre (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-structure questionnaire. From those answers, it resorts that all physicians (100%) and pharmacists (100%) had already suspected at least one time ADR in their practice. Particularly for antimalarial drugs 30.77% physicians versus 31.11% pharmacists faced at least one time ADRs. Physicians as well as pharmacists (0.0%) had never reported ADRs to pharmacovigilance service. However, 50.77 % of physicians versus 48.89% of pharmacists had 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 PV.
Any ADR reporting form was available neither at the side of physicians as well as at pharmacist side.
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”, lack of knowledge of how to reach ADR forms” (Table **1**).

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

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	

Knowledge, attitudes and practices of representatives or delegates of the pharmaceutical companies to adverse drug reaction reporting in Benin

A minor proportion (6.97 %) of representatives of the pharmaceutical companies monitor at regular basis the ADRs of their medicines. In the absolute majority (100 %) they indicate that reporting was done to their headquarters but not to MoH of the country. 39 of 43 indicated that their laboratories have internal pharmacovigilance system.
Any of these laboratories have well defined pharmacovigilance system based in Africa or in Benin.
Any ADR reporting was done to the DPM by the representatives of the pharmaceutical companies and then any laboratories have experienced the drawback of its product from market.
All laboratories have never received report 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
Several sessions with this focus group helped to review different documents (Policies, laws, Standard operation procedures and working instructions documents) and discussed with them. In Benin, there is one service 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 quantity and quality i.e skills) 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 postmarketing surveillance and pharmacovigilance important aspects of medicines registration and selection in Benin. The following pharmacovigilance legal documents are available: 1. Order No. 1801/MS/DC/SGM/CTJ/DPM/SA of February 20, 2007 defining functions, Organization and Functioning of the Direction of Pharmacies and Medicines of Benin. Article 11 defines the tasks of the service of Pharmaceutical Inspection and Pharmacovigilance.
Pharmacovigilance -related policy is being part of this global document.
2. Order No. 4182/MSP/DC/DPHL/SPM setting duties and functioning of the Technical Committee on Drugs.
3. Existence of ADR form
However, there is 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 developped 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 CTAs in particular but only before market releasing. There is no set schedule for quality control of antimalarial drugs and CTAs in particular**. Control quality of antimalarial drugs has** not taken place regularly due to events or circumstances; usual sites of sampling for quality control are: health centers, area hospitals, pharmacies, the NMCP, donations. Relations with the NMCP and PV 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 uncertain (ASS, 2008), reliable testing of ACTs is not always affordable due to diverse reasons: lack of solvents, lack of control products or internal standards or lack of financial resources. Some proposals to improve this aspect of pharmacovigilance of ACTs are: systematic testing prior importation and before the availability of ACTs in the distribution chain, awareness on the harmful effects of self-medication.

Interview with the leaders of hospitals
Three different sessions were held with the Director of CNHU. It shows that:
There is no committee to monitor ADRs in the hospital. PV activities are, for now, lacking 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. Filings spontaneous adverse events are not yet available to the CNHU. However, officials have met with the DPM CNHU authorities to set up a pharmacovigilance structure and wished also met the CMC. The Director of CNHU showed high interest for PV and hoped that the center referee CNPV whom he considers to be an essential structure of health protection for the entire country.

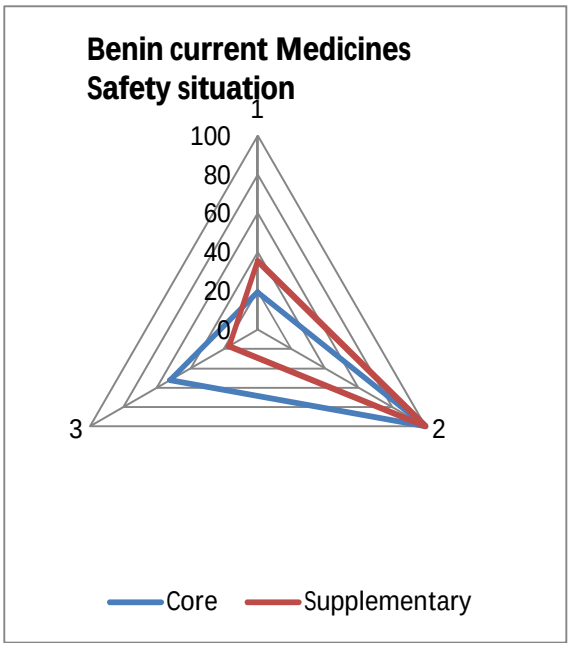
Systems, Structures, and Stakeholder Coordination
Using the indicator-based assessment tool (SPS 2009), collect data at the MoH (DPM), NMCP (PNLP), LNCQ and at the biggest teaching hospital (CNHU), the findings is presented in Figure **1**. Each “Yes” on a core indicator is given a score of 2**;** each 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 which should be done.

Table **2** and Figure **1** show clearly that there is national pharmacovigilance unit with mandate and structure is lacking meaning that there is no national pharmacovigilance coordinating center. There are no functional information and technology infrastructure. We also notice lack of ADR forms for health professionals to report.

Benin is an associate member of WHO Collaborating Centre for International Drug Monitoring since many years illustrating the stagnation of pharmacovigilance deployment in the country**.**
Findings using IPAT is shown in Table 2 and Figure 1.

Table 2 & Figure 1: Assessment of Pharmacovigilance and Medicine Safety System in Benin using IPAT

Indicators	Score	Benin	Max	
1,1	Core	2	2	
1,2	Core	0	2	
1,3	Supplementary	0	1	
1,4	Supplementary	0	1	
2,1	Core	0	2	
2,2	Core	0	2	
2,3	Core	0	2	
2,4	Core	2	2	
2,5	Core	2	2	
2,6	Core	0	2	
2,7	Core	0	2	
2,8	Core	0	2	
2,9	Core	0	2	
2,10	Core	0	2	
2,11	Supplementary	0	1	
2,12	Supplementary	1	1	
2,13	Supplementary	1	1	
2,14	Core	0	2	
2,15	Supplementary	1	1	
3,1	Core	0	2	
3,2	Core	0	2	
3,3	Core	2	2	
3,4	Core	2	2	
3,5	Core	0	2	
3,6	Core	0	2	
4,1	Supplementary	0	1	
4,2	Supplementary	1	1	
4,3	Supplementary	0	1	
4,4	Core	0	2	
4,5	Core	0	2	
4,6	Core	0	2	
4,7	Core	0	2	
4,8	Supplementary	0	1	
5,1	Supplementary	0	1	
5,2	Supplementary	1	1	
5,3	Supplementary	0	1	
5,4	Supplementary	0	1	
5,5	Supplementary	0	1	
5,6	Supplementary	0	1	
5,7	Core	0	2	
5,8	Core	0	2	
5,9	Supplementary	1	1	
5,10	Core	0	2	
	Core	**19**	100	52
	Supplementary	**35**	100	17



Overall 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

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	
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

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

Different cascade of trainings led by NMCP and Faculty of Medicine in the frame of management of severe malaria were also provided to health professionals.

Donor community were sensitized and supportive to the need for PhV system.

Besides 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.

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

Interests for pharmacovigilance have gradually been gaining attention. Different organizations such as NGO were interested in getting involved. Africare has included in its action plan a number of activities to strengthen the system of pharmacovigilance: 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. Similar activities were also planned by the Catholic Relief Services (CRS).

DISCUSSIONS & 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 in Africa) with the aim to perform situational analysis involving all stakeholders and majority of aspects related to the control of ACTs safety.

Pharmacovigilance has gained wide global interest since the 1990s illustrating by the number of reports in the WHO global ICSR database as well as the number of countries joining the WHO Pharmacovigilance programme (Olsson S et al., 2010). Despite this global progress, the situation in Benin is still alarming. A national pharmacovigilance reporting system is non-existent. The situation is also not really promising 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 (Kuemmerle A et al., 2011). Those reports were all sent to UMC after the WHO recommendation to use ACT for uncomplicated malaria was published in 2001 (Report of a WHO Technical Consultation Geneva; 2001).

Identification of the main barriers and weakness lead to make recommendations for towards establishment of an 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 independent National Pharmacovigilance and Medicine Information Center (NPMIC). For instance the inclusion of Pharmacovigilance in Pharmaceutical Inspection service should be clearly avoided and constitute a major pitfall knowing that Pharmaceutical Inspection is itself a dense activity and is not assumed properly today (ASS, MSB, 2008). The establishment of a NPMIC with well-defined organization chart will be a key to success. Autonomous status with assigned goals should allow to the center the capacity to succeed by increasing its visibility**.** In addition, the formalization of a technical committee of pharmacovigilance (see organization chart in Figure 2) will help to define agenda and enable related activities.

In general, pharmacovigilance is a multidisciplinary issue that involves disciplines such as clinical pharmacology, clinical medicine, toxicology, epidemiology and genetics (Oshikoya KA et al, 2010). Unfortunately, expertises in these disciplines are few in Benin and this should lead to adequate human resources use. 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. Jobs descriptions, tasks and responsibilities of the Staff should be defined. A qualified person for pharmacovigilance (QPPV) should be identified also at the regulatory side such as MoH. It is not convincing that a 4-day training given to the focus was enough to make them experts in PhV or make them competent to accurately assess the causality between the reported adverse events and the drugs (Oshikoya KA et al, 2010). Emphasize that the major shortcoming is the lack of expertise and non-continuity of the business at the time of this assessment. Thus efficient pharmacovigilance systems that consist of strong expertise should be constituted.

It is desirable to ensure strong link between the NPMIC and the Faculty of medicine as the pharmacology unit provide PhV training to Pharmacy and Medicine Students. In consequence students such as Intern and Externs in Medicine and Pharmacy could help to ensure a permanent activity of the NPMIC.

Developed countries such as France used this strategy to have students in regional pharmacovigilance centres by giving them the opportunity to learn by doing. In order to ensure effective functionality of the NPMIC, it is desirable that it benefits from the expertise of human resources pool available in the country. NPMIC should collaborate extensively with clinicians from different specialties and with academia and drug research units. Consequently, it is recommended to establish a multidisciplinary “technical Committee” to assist NPMIC on technical matters**.** Given all the arguments developed above, it is completely realistic and more efficient to implement NPMIC at the biggest teaching Hospital or at Faculty of Health Sciences.

The clinical pharmacology unit of the Faculty of Medicine should then provide rallying points for the mobilization of technical expansion of pharmacovigilance in the country. Previous successful examples have seen in South Africa, Zambia, Maroc etc... The National Adverse Drug Events Monitoring Centre (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. France pharmacovigilance system is also a fantastic example of success of this system where universities play a key role. This approach shows clearly its power to fill the expertise gap. 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 an active system of Pharmacovigilance of ACT. A prospective cohort study tracking patients on ACTs could be the start point letting to have rapidly overview of those drugs safety in Benin population. Active studies in target groups such as pregnant women, children under 5 years active-studies can be conducted in sentinel sites or in some health centres.

An elaboration of Pharmacovigilance system is an essential step. Different health systems are already established in the country such as SNIGS or epidemiological surveillance system (ESS). The pharmacovigilance system could be based on one of those available systems with some adaptations. 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**.
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 on “medicines safety” from early.

Education and Training of Health Professionals on Pharmacoviglance and ADRs reporting
Ohaju-Obodo JO & Iribhogbe OI (2010) found similar results about health professionals experience related to ADRs (92.4% vs 100% in our study). 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 suprastructure and highly visible National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria. The 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 centre, lack of awareness of pharmacovigilance systems. Similar reasons were found in previous studies from different countries (Hale Zerrin Toklu & Meral Keyer Uysal, 2008; Hazell and Shakir, 2006).

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 to take care of uncomplicated malaria. Different 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 professionals in the private sector have not undergone training on PV. Among those who have already undergone training in PV (especially among the general public), the objective will be to maintain high rate reporting of ADRs. Local strategies to stimulate reporting on ADRs should be developed and implement at beginning.

Improve Quality control by strengthening Pharmaeutical Inspection
Quality Control of ACTs should be improved by increasing the number of inspections in Wholesalers, in pharmacies or in deposits located in the private or public health centers, deposits at community level. All links in the chain distribution should be inspected regularly. For this purpose an agreement between the NMCP and LNCQ should be defined with planned activities. The country should join the agreements PIC (Pharmaceutical Inspection Convention) and follow this convention.
At the time of this study was done, artemisin monotherapies are still present on the market (Personal communication). Planned and gradual withdrawal of monotherapy should be implemented.

Monitoring of ACTs resistance
The rapid increase of antimicrobial-resistant strains for both established and new-generation of drugs makes drug resistance a global problem (Huff-Rousselle M et al, 2007). This is a broader and more critical threat in African countries because, in addition to antibiotics, this continent disease burden is heavily

biased toward three infectious diseases particularly susceptible to the rapid development of resistance: HIV/AIDS, malaria, and tuberculosis (Huff-Rousselle M et al, 2007).

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. A number of efficacy studies per year should be defined also according to the availability of resources. The monitoring of ACTs resistance activities could be conducted on sentinel sites. The sites will be selected in such a way as to have a variability rate of self-medication, the penetration rate of ACTs and therapeutic arsenal. Information obtained through those types of study could then be used to direct scientific analyses of reported adverse events and reactions. In other hand, early warning signal development of drug resistance could be generated from spontaneous database reporting. We should remind here that treatment failure is also adverse drug reaction and should be reported like that during the spontaneous reporting procedure. It is desirable that NMCP collaborate with research institutions to achieve these goals.

In the same way, the public education of health professional and patients to increase the rational use of ACTs should be maintained. ACTs should be integrating in the circuit and the list of essential drugs. Periodic evaluation of knowledge, perceptions and attitudes vis-à-vis ACTs should be performed regularly.

In general, promotion of rational use drugs such as ACTs could succeed only if the whole process of rational use of all drugs authorized in the country is on track. The national therapeutic guide or compendium, flowcharts for therapeutic management development and its dissemination for physicians and health professionals should 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).

The reinforcement of the Technical Committee of Registration of Medicines and the global structure of drug regulation should be reviewed and reinforced with adequate qualified human resources. The creation of a drug agency will give greater visibility to all activities related to pharmacovigilance, quality control and monitoring of drug efficacy in general and especially of ACTs.

The lack of staff trained in pharmacovigilance seems to be the most serious limiting factor for the development of pharmacovigilance in Benin. For instance, only one person at MoH was devoted to pharmacovigilance at DPM. Competencies in cross-cutting scientific areas (Pharmacology, epidemiology, clinical sciences etc…) are normally required in carrying out pharmacovigilance functions.
Several international agencies are also stepping in with various programmes and activities to support pharmacovigilance in developing countries. Different missions and different activities were initiated by all these agencies for Benin without solid achievement so far. This lack of results is due to the fact there are no local competencies in pharmacovigilance service at MoH. We forget usually that pharmacovigilance is research activities. Strangely, these competencies are present in all these countries where clinical pharmacology department exist at Faculty of medicine or Faculty of Health Sciences. The most impactful and durable solution is to used local competencies or local human resources to achieve this. Unfortunately in many low-income countries, activities of MoH including pharmacovigilance for example are separated from academic institutions. The MoH does not use enough the expertise available in academic institutions to achieve the objectives assigned to it. It is important to address this lack of commitment to patient safety in Benin. Immediate follow-up activities should be implemented to address these gaps highlighted through this assessment.

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 sector. The country recognized 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 NPMIC with qualified persons is a prerequisite. Transparency in the recruitment of expertise of pharmacovigilance and the head of NPMIC must always be ensured. 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 report is a reference to benchmark the progress overtime.

Abbreviations

ADR: Adverse drug reaction; WHO: World Health Organisation; CNH-HKMU: Centre National Hospitalo-Universitaire Koutoukou-Maga; NPC: National Pharmacovigilance Centre; NAFDAC:
National Agency for Food and Drug Administration; IQR: Interquartile Range and Control;
OTC: Over The Counter; PhV: Pharmacovigilance; ACTs: Artemisinin-based combinaison therapy; NPMIC: National Pharmacovigilance and Medicine Information Center
MoH: Ministry of Health; NGOs: Non Gouvernemental Organizations;
IPAT: Indicator-based Pharmaceutical 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: The WHO Programme for International Drug Monitoring, the Uppsala Monitoring Centre

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Figure 2: Proposal organization chart of the NPMIC and relations with other stakeholders

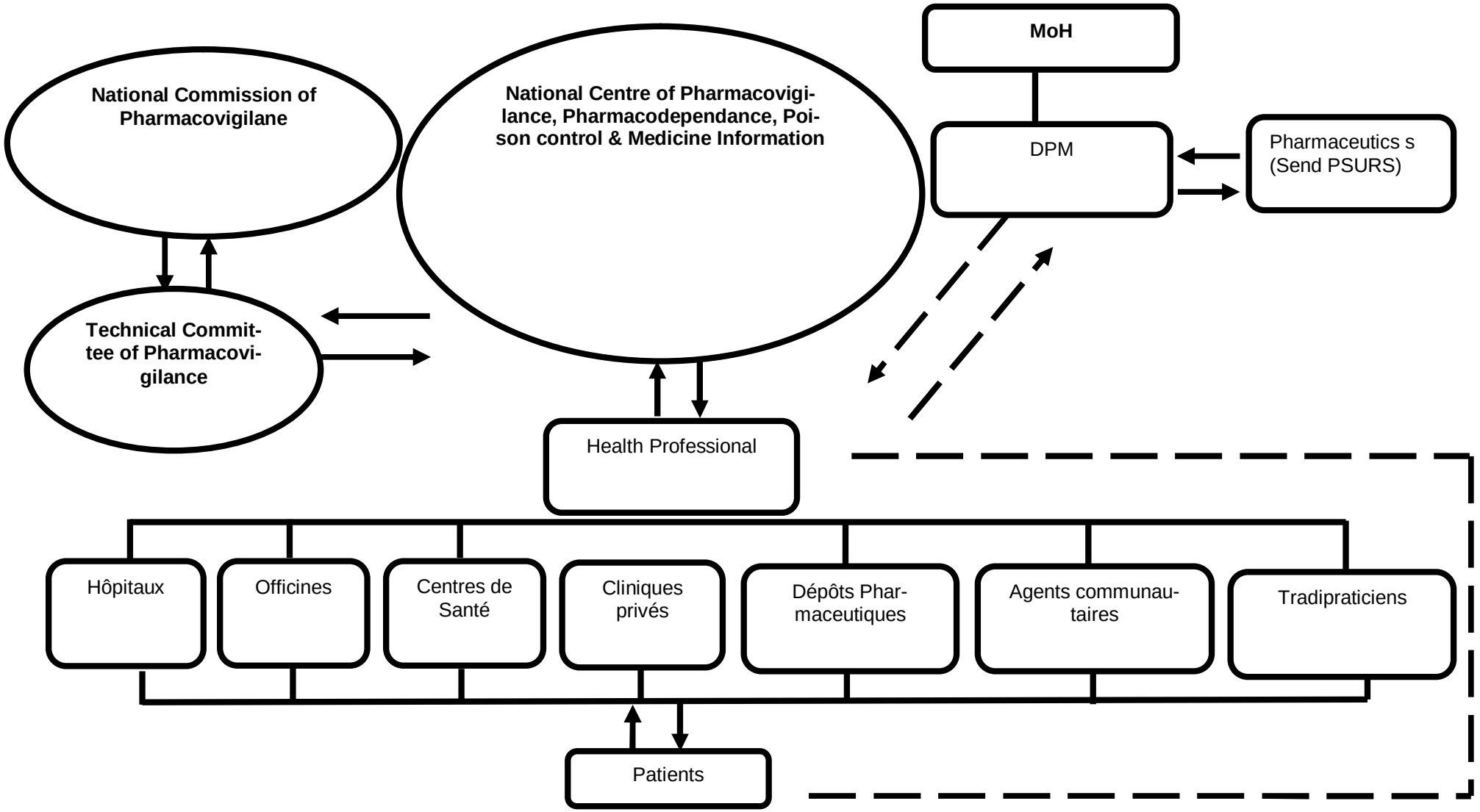

Figure 3: Proposal health system (based on epidemiologic surveillance system with minor modifications) to collect ADRs