Evaluation of pharmacovigilance system performance in South- South Nigeria

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THESIS PRESENTED TO OBTAIN THE GRADE OF

DOCTOR OF THE UNIVERSITY OF BORDEAUX

Doctoral School, SP2: Society, Politic, Public Health Specialisation Pharmacoepidemiology and Pharmacovigilance

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EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH- SOUTH NIGERIA

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Acknowledgements

This dissertation could not have been possible without God my maker, creator and author of my life; to Him I owe it all. A journey of a thousand miles starts with a first step. It has been a trip of many first steps; the doctoral program is one that requires dedication, an aim to finish and good mentorship.

I acknowledge my theses directors- Prof Ambrose Isah, who has been a father, a mentor, a supervisor, an uncle rolled into one. He always reminded me of the finish line even in the midst of difficulties. Prof- I didn't know what I knew until it was needed. Thank you for all the encouragement from the application to the point of this defence. Truly grateful. I also thank his wife, Prof Essy Isah who stood with me and by me when I needed help. God bless you.

When your path crosses a charming supervisor, hold on tight. My progress was assured in the Eu2P program when Annie Fourrier-Réglat was made my supervisor. She anticipated my difficulties, simplified issues that seemed gargantuan and was always available by calls, email, Skype. I never had to wonder about the direction of the program, she and Prof Isah kept me focused. Truly I was blessed to have been paired up with her. Merci. I equally thank the staff and members of the pharmacoepi department of the University of Bordeaux. They always went out of their way to make my visits pleasant and memorable. The Eu2P office- I am truly grateful for the administrative support. No request was too big or too mundane. Merci…

I also thank the Jury Members- Prof Ray Ozolua, Prof David Nicholas Bateman, Prof Ralph Edwards and Prof Nicholas Moore for their excellent review and kind words during the defense.

Dr. Stephen Ayinbuomwan, my friend, colleague and brother at the department of Clinical Pharmacology and Therapeutics, University of Benin, has been there through it all. Ever ready to hold fort when I had to go for field work, he also provided qualitative advice and spiritual support. Thank you. The other members of staff of the department of Clinical Pharmacology and Therapeutics, the staff (Consultants, residents and house-officers) of the department of Internal Medicine, University of Benin/University of Benin Teaching Hospital, the staff of the zonal pharmacovigilance centre, my research assistant Joyce Idahosa that contributed to the various aspects of the thesis. I am immensely grateful. Indeed I am grateful to Prof. L.I.Ojogwu (Professor Emeritus) of the department of Medicine who ignited my interest in Internal Medicine when I was an undergraduate medical student in the University of Benin and encouraged my academic development. Thank you for your interest.

The Chief Medical Directors (past and present) of the various tertiary hospitals, the administrative staff, medical records staff as well as all the participants. The study was indeed possible because of your kind approval and participation. Thank you. Special mention goes to members of the pharmacovigilance committees of the various institutions especially Pharmacist Ekpeyong, Pharmacist Effiong, Pharmacist Omuso Obrasua, Pharmacist Ejiro Akpovwovwi, Pharmacist Mogon-Barthy and Pharmacist Tudgegbe for their kind help. I also acknowledge the help of Drs. Nwafor, Dr. Udoh, Dr. Okpa, Dr. Ukweh, Prof Akpa, Prof. Okpani, Dr. Nkem Okoli, Dr. Phil Onuwaje, Dr. Mankwe, Dr. Jombo, Dr. Roy Aghwana, Dr. Okoye, Dr, Atoe-Percy, Dr.Slater, Dr.Uwaila, Barr. Onwuozeobe, Dr. Sally, the Deputy Directors of Nursing services, the Deputy Directors of Pharmacy services as well as the top

management and staff of the various hospitals. The ethics and research committee reviewers who gave useful advice prior to commencement of the research. Thank you.

My parents, Chief Philip Oyebanji and Mrs. Helen Tinuola Olowofela have always encouraged me to be the best and not give up. Thank you for the physical and emotional support.

I am blessed to have another set of parents in my aunt Femi and uncle Joe Akpede, thank you for being supportive. My friends Ranti, Bukky, Doyin, Gbodi, Esosa, Jennifer, thank you for being my friends and being always ready to help.

My siblings- Lola, Nike, Folake, Tayo, Toyosi, you have been great. Obuks, Tega, Ese, Seun. My in-laws- the Opadeyis. Thank you all for the immense support.

My dear husband- Bayo and my darling daughters- Oreofe and Idara, thank you for bringing the sunshine into my day. Thank you for the love, care, affection and forbearance during the course of the study.

To God be the glory.

Abimbola

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Abstract

The evolution of the pharmacovigilance system in Nigeria has been associated with modest growth and teaching hospitals have been identified as important partners in the pharmacovigilance mechanism. However, there have been no studies evaluating the performance of the pharmacovigilance system in Nigerian Teaching hospitals prior to this time. This study set out to evaluate the state of pharmacovigilance specifically adverse drug reactions in South-South Nigeria. The pharmacovigilance system as well as the prescribing pattern of medicines was evaluated using the WHO Core Pharmacovigilance indicators and WHO Core Prescribing indicators respectively. This was followed by an educational intervention with text messages sent via the Short Messaging System (SMS) to improve the knowledge, attitude and practice of pharmacovigilance amongst healthcare professionals. The number, quality and profile of Adverse Drug Reactions (ADRs) were also assessed before and after the intervention. Factors likely to contribute to poor reporting of pharmacovigilance issues were sought by conducting knowledge, awareness, and practice survey of healthcare professionals working in the zone.

The findings showed that of the six teaching hospitals assessed, only three could be described as functional or partly functional although all had some structures in place for pharmacovigilance activities. The process and outcome/impact indicators revealed weak health systems and overall insufficient attention to pharmacovigilance in the hospitals as only one centre had committed their ADR reports to the National Pharmacovigilance Centre and there were few documented medicines related admissions ranging from 0.0985/1000 to 1.67/1000 admissions. It further showed that although a modest knowledge and fair perception of pharmacovigilance existed among the group, practice was poor as only 12% of the 811 healthcare Professionals had ever used the national ADR reporting form and there were few adverse drug reaction reports in the local hospital databases. These were attributed to insufficient awareness of pharmacovigilance on what can be reported, poor reporting processes, wrong beliefs that their reporting will not make a difference and difficulty in determining what to report. There was an improvement in the knowledge and practice of pharmacovigilance, with a 31.6% increase in the number of adverse drug reaction reports following an educational intervention. This study also highlighted the ADR profile to commonly used medicines in the zone and the inherent problems associated with spontaneous reporting. It further highlights that the growing discipline of pharmacovigilance can be improved through frequent assessments of the system, training of the healthcare professionals and general strengthening of the Nigerian healthcare system. More in-depth studies would be required to further evaluate the safety of medicines in the Nigerian population.

Key word: Pharmacovigilance, Adverse Drug Reactions, Healthcare Professionals, Educational intervention, Health knowledge and attitudes, Pharmacovigilance Indicators, Quality, Pharmacovigilance system, Nigeria.

Résumé

L'évolution du système de pharmacovigilance au Nigéria a été associée à une croissance modeste et les hôpitaux universitaires ont été identifiés comme des partenaires importants du système de pharmacovigilance. Cependant, aucune étude n'a encore été réalisée sur les performances du système de pharmacovigilance dans les hôpitaux universitaires nigérians. Cette étude visait à évaluer l'état de la pharmacovigilance, en particulier les réactions indésirables aux médicaments dans le sud et le sud du Nigéria, en se référant à des médicaments sélectionnés. Le système de pharmacovigilance ainsi que le schéma posologique des médicaments ont été évalués à l'aide des indicateurs de pharmacovigilance de base de l'OMS et des indicateurs de prescription de base de l'OMS, respectivement. Cela a été suivi d'une intervention éducative avec des messages texte envoyés via le système de messagerie courte (SMS) pour améliorer les connaissances, l'attitude et la pratique de la pharmacovigilance parmi les professionnels de la santé. Le nombre, la qualité et le profil des effets indésirables du médicament ont également été évalués avant et après l'intervention. Les facteurs susceptibles de contribuer à une mauvaise notification des problèmes de pharmacovigilance ont été recherchés en effectuant une enquête sur les connaissances, la sensibilisation et les pratiques des professionnels de la santé travaillant dans la zone. Ces faiblesses de la pharmacovigilance étaient essentiellement.

Les résultats ont montré que sur les six hôpitaux universitaires évalués, seuls trois pouvaient être décrits comme fonctionnels ou partiellement fonctionnels, bien qu'ils disposaient tous de certaines structures pour les activités de pharmacovigilance. Les indicateurs de processus et de résultat / impact ont révélé des systèmes de santé défaillants et une attention générale insuffisante accordée à la pharmacovigilance dans les hôpitaux, un seul centre ayant envoyé ses rapports d'effets indésirables au Centre national de pharmacovigilance et peu d'admissions documentées liées aux médicaments allant de 0,0985 / 1000 à 1,67 / 1000 entrées. Il a également montré que, même si le groupe possédait une connaissance modeste et une perception juste de la pharmacovigilance, la pratique était médiocre 12% seulement des 811 professionnels de la santé ayant déjà utilisé le formulaire de notification des effets indésirables associés aux médicaments et peu de réactions indésirables au médicament étaient répertoriées dans les bases de données des hôpitaux locaux. Ces faiblesses ont été attribuées à une connaissance insuffisante de la pharmacovigilance sur ce qui peut être signalé, à des processus de notification médiocres, à de fausses croyances selon lesquelles leur notification ne fera aucune différence et à la difficulté de déterminer les éléments à signaler. Une perception insuffisante de l'intérêt de la notification des effets indésirables. Les connaissances et les pratiques en matière de pharmacovigilance se sont améliorées, de même que le nombre de déclarations d'effets indésirables au médicament suite à une intervention éducative. Cette étude a également mis en évidence le profil des effets indésirables associés aux médicaments couramment utilisés dans la zone et les problèmes inhérents à la notification spontanée. Il souligne également que la pharmacovigilance, discipline en pleine croissance, peut être améliorée par des évaluations fréquentes du système, la formation des professionnels de la santé et le renforcement général du système de santé nigérian. Des études plus approfondies seraient nécessaires pour mieux évaluer la sécurité des médicaments dans cette population Nigeriene.

Mots clés: pharmacovigilance, professionnels de la santé, intervention éducative, connaissances sur la santé, attitudes, indicateurs de pharmacovigilance, qualité, système de pharmacovigilance, Nigéria.

List of Abbreviations

ACEI	**-**	Angiotensin Converting Enzyme Inhibitors
ACT	-	Artemisinin Combination Therapy
ADR	**-**	Adverse Drug Reaction
ATC	-	Anatomic Therapeutic Chemical classification
DELSUTH	**-**	Delta State University Teaching Hospital Oghara, Delta State,
EMA	-	European Medicines Agency
EML	-	Essential Medicines List
EU	-	European Union
FMoH	-	Federal Ministry of Health
GVP	-	Good Pharmacovigilance Practices
HCP	**-**	HealthCare Professional
ICSR	**-**	Individual Case Safety Report
IPAT	**-**	Indicator based Pharmacovigilance Assessment Tool
ISOP	-	International Society of Pharmacovigilance
KAP	**-**	Knowledge, Attitude and Practice
MAH	-	Marketing Authorisation Holders
MedDRA	-	Medical Dictionary for Regulatory Activities
NAFDAC	**-**	National Agency for Food, Drugs Administration and Control, Nigeria
NDSAC	-	National Drug Safety and Advisory Committee
NDUTH	**-**	Niger Delta University Teaching Hospital Okolobri, Bayelsa State
NPC	-	National Pharmacovigilance Centre
PRASCOR	-	Pharmacovigilance Rapid Alert System for Consumer Reporting
PV	-	Pharmacovigilance
PVG/FDC	-	Pharmacovigilance/Food and Drug Information Centre
PSUR	-	Periodic Safety Update Report
SOC	-	System Organ Classification
SMS	-	Short Messaging Service
SSFFC	-	Substandard, Spurious, Falsely Labelled, Falsified and Counterfeit

STG	-	Standard Treatment Guidelines
UBTH	-	University of Benin Teaching Hospital Benin-City, Edo State
UCTH	-	University of Calabar Teaching Hospital, Calabar Cross-River State
UPTH	-	University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State
UUTH	-	University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State.
US FDA	-	US Food and Drug Administration
WHO	-	World Health Organisation
WHO-PIDM	-	WHO Program for International Drug Monitoring

GENERAL INTRODUCTION

General Introduction

Pharmacovigilance and the pharmacovigilance system definitions

According to the World Health Organisation WHO "*Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems*" [1]. It is a developing discipline especially in the developing nations where medicines are perceived as beneficial and not harmful. The development of Pharmacovigilance (PV) as an entity has been accompanied by near cataclysmic occurrences in the world and the earliest recorded episode can be traced to the 15th century [2]. The thalidomide disaster of 1961[3] brought to the fore the need for continued vigilance in the post-marketing phase of a medicinal product as well as the need for health care professionals to develop a high index of suspicion in recognising adverse drug reactions and report such reactions spontaneously in a systematic approach that will yield the maximum benefits.

According to the module I of the Good Pharmacovigilance Practices (GVP) of the European Medicine Agency (EMA), a pharmacovigilance system is defined as "*a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk benefit balance [DIR Art 1(28d)*" [4]. The pharmacovigilance system should have in place structures, processes and outcomes in order to achieve its objectives. Any organisation that is involved in the collection, documentation and transfer of Individual Case Safety Reports (ICSRs) needs a functional pharmacovigilance system [5]. This need stems from the understanding that systematic coordination of pharmacovigilance is necessary to mitigate the burden that ADRs occurrence imposes on patients and the society at large.

Internationally, WHO serves as the coordinating body for pharmacovigilance activities worldwide with the WHO Program for International Drug Monitoring (PIDM) centre domiciled in Uppsala. They perform a number of roles including the coordination, detection and assessment of Adverse Drug Reactions (ADRs), causality assessments, provide risk minimisation plans and also ensure effective communication of potential risks and signal detection. They also give guidance towards establishment of national pharmacovigilance systems [6]. The contributions of different member countries has increased the number of ADRs stored in the WHO database (Vigibase™) which stood at 16,720,000 million as in February 2018. Each country was admitted into the PIDM based on submission of ADR reports to the WHO database and for meeting other necessary requirements. However, organisation and quality of pharmacovigilance systems may vary from country to country and sometimes region to region. There are presently 158 countries (131 full, 27 associates) in the WHO monitoring program [7].

The pharmacovigilance system in the developed nations share a common trait of having enabling legislation to undertake the pertinent pharmacovigilant activities, relevant infrastructure and in most of those countries, electronic databases and reporting systems, they also have strategies for effective signal detection and well laid out pharmacovigilance communication plans. The strength of PV systems still lies in spontaneous reporting of ADRs and therein lies the limitation, which is that of under-reporting [8].

Different models of the PV system exists with regionalisation of PV centres in some countries [9,10], national PV centres independent of the regulatory body, mandatory reporting of adverse drug reactions by healthcare professionals, as well as reporting by various cadres of healthcare professionals. All of these is manifested in the number and good quality of reports which are in excess of thousands yearly in some of those countries [8,11].

The African PV system is grossly underdeveloped, as the continent grapples with a number of socio-economic and health challenges, inadequate financial budget for health systems. The pharmaceutical scenario is awash with issues relating to inadequate manufacturing pharmaceutical units, poor distribution practices, limited access to medicines due to cost and logistic considerations. Furthermore, the irrational use of medicines, presence of substandard falsified medical products that dot the African pharmaceutical landscape makes it even worse [12,13]. Various African countries have in place legislature of varying degrees to combat the above concerns and recently, there have been moves to establish an African Medicines Agency to harmonise the various intercontinental approaches to drug and patient safety. Measuring the impact of the various PV systems had been a major limitation and these resulted in the development of tools set out to enable PV centres perform self-assessment and improve their systems [14,15].

The Nigerian pharmacovigilance scenario-burden and characteristics

Nigeria belongs to the lower-middle income nations as defined by the WHO [16] and it is also classified as a developing nation. It is a highly populous country in West Africa with a population of approximately 190 million and with diverse ethnic groups. It is administratively split into 36 states and a Federal Capital Territory; there are also six geo-political zones- North-East, North-West, North-Central, South-West, South-East and the South-South zones. The South-South Zone which is the area under focus in this research is located in the coastal region of the country and comprises six states namely Akwa-Ibom, Bayelsa, Cross-Rivers, Delta, Edo and Rivers States. It is home to about 21 million residents according to the last National census of 2006. Nigeria has a high burden of both communicable and non-communicable diseases [17] with non-communicable diseases noted to be on the increase [18]. It is important to critically evaluate the safety of medicines used in such an environment and also to review the medicines used in managing diseases that have high prevalence rates. The age adjusted mortality rate by cause for communicable diseases according to the WHO 2013 statistics in Nigeria was reported to be about 832 per 100,000 with the major contributors being malaria, respiratory infections, HIV, diarrhoeal diseases and non-communicable diseases also had a rate of 756.7 per 100,000 in the same report [17].

Treatment of infectious diseases should follow the standard treatment guidelines and rational pharmacotherapy, however, self-medications is commonplace with analgesics and antibiotics in Nigeria, due to the availability of most analgesics as Over The Counter (OTC) medicines and poor restriction of antibiotics procurement and usage [19–21]. With the common use of these medicines, it is suspected that there may also be an associated high prevalence of adverse drug reactions. The burden in economic terms has also not been fully quantified. However, considering the irrational medication use practices observed [22], the burden is bound to be immense. The practices in the different zones of the country may vary in line with the ethno-cultural influences of the zone and presently, the extent of irrational prescribing practices in the South-South zone is unknown. There is also a paucity of studies in the Nigeria setting that have described the Adverse Drug Reactions (ADRs) profile to these commonly used classes of medicines.

Nigeria became the 74th country to join the WHO International drug monitoring programme in 2004 [23] and has developed its own pharmacovigilance system with the introduction of pertinent policies [24–26], the creation of zonal centres, institutionalisation of PV in health institutions, consumer reporting among others [27]. The governance of pharmacovigilance in Nigeria is situated from the National Pharmacovigilance Centre (NPC) and involves the zonal centres, academic institutions and marketing authorisation holders [27]. They all have specific roles and functions that are vital to the development of

drug safety in Nigeria. The NPC is yet to achieve the WHO recommended target of receiving 100 ADR reports per million as there is a total of about 18,000 ADR reports in the database as at 2017, it is however still inadequate. This may be attributed to the developing nature of the Nigerian pharmacovigilance system. Factors contributing to this poor reporting of ADRs have previously preliminarily been explored mainly at single institutions scattered around the country, none at the Zonal level and very few in the South-South zone of the country [28–33]. Those studies also concentrated mainly on physician reporters and ADRs reporting. Although the NPC guidance document states that nurses can report, few studies have evaluated the perception of nurses towards ADRs reporting in Nigeria. Those studies did not explore the other facets of pharmacovigilance (e.g.: scope and product concerns). In this context, it is important to evaluate the perception, practice of the health care professionals in South-South Nigeria towards these issues in view of the recent creation of the South- South Zonal Pharmacovigilance Centre. Again patient reporting is being encouraged worldwide and various methods are being evaluated on how best to ensure quality and completeness of the ADR reports[34,35]. Indeed in some centres it has been shown that patient ADR reports are comparable with those from the health care professionals[36]. Therefore it is important to study the types of reactions described by patients to commonly utilised medicines in this setting in order to evaluate the possible contributions of patient reporting to the pharmacovigilance system in Nigeria. Already a form of consumer reporting is being encouraged through the use of the Pharmacovigilance Rapid Alert system for Consumer Reporting (PRASCOR), this utilises text messages sent directly to the NPC for evaluation. However, it is important to evaluate methods that may be useful to the healthcare professionals as well so as to ensure that adequate documentation is made and also to avoid complications that may arise from an inadvertent rechallenge.

The weaknesses discovered in the pharmacovigilance systems in Africa and indeed Nigeria are majorly lack of expertise, poor infrastructural set up as well as inadequate resources being committed to pharmacovigilance [37]. Other identifiable problems include substandard falsified medical products that lead to therapeutic ineffectiveness, adulteration of medicines, faulty drug distributions systems, use of herbal medicines and development of drug-herb, drug–food interactions[12,37]. Other issues relating to pharmacovigilance such as medication errors, poisoning (acute and chronic), drug abuse and misuse of medicines have not also been properly quantified. According to the pharmacovigilance indicators developed by WHO, the use of standard indicators in measuring the effectiveness of a pharmacovigilance system would be helpful in determining the state of pharmacovigilance activities in that setting[15].

Characteristics of Adverse Drug Reactions in Nigerians

In established pharmacovigilance systems, use of electronic databases to evaluate harm from the use of medicine in the population is fast becoming an important tool in pharmacovigilance. In addition to the spontaneous adverse reaction reporting methods this has remained useful in signal detection[38]. Characterisation of the ADRs profile in Nigeria largely depends on spontaneous reports as there is a dearth of such electronic databases. Most of the available literatures are case reports or case series which focuses on single therapeutic agents or classes. The homogenous nature of the Nigerian population makes it imperative to study in-depth the ADRs which may have occurred in this area. The impact of the occurrence of ADRs include poor adherence to therapy, increased economic cost; increased morbidity and mortality[39]. The consequences of these outcomes for the healthcare system of a developing country are enormous. Unfortunately, the profile of

ADRs to these medicines have not been well characterised. For example, anecdotal reports suggests higher rates of angioedema and cough following the intake of Angiotensin-Converting Enzyme Inhibitors ACEI(s)[40] and an increased frequency of micturition observed with among the Calcium Channel Blockers, the dihydropyridine derivatives [41].

The incidence of ADRs varies among different races as shown in a meta-analysis published in 2006 that studied ethnic differences in the development of ADRs to cardiovascular medicines. A slightly higher proportion of some types of ADRs was found in blacks and hispanics as compared to the non-black population [42]. Determinants of these differences are unknown and there is a need to properly characterise these ADRs in the Nigerian population.

Overall there is a dearth of data regarding pharmacovigilance of commonly used medicines in Nigeria. Further studies are still required to properly characterise the profile of pharmacovigilance activities in this ethno-racial group.

Aims and objectives of the thesis

The aim of this thesis was to evaluate the state of pharmacovigilance specifically ADRs in South-South Nigeria with reference to selected medicines. To achieve this aim, we sought to determine what the state of pharmacovigilance was in teaching hospitals in South-South Nigeria. We also needed to find out what the knowledge, attitude and practice of health care professionals was towards pharmacovigilance. Furthermore, what was the profile of ADRs in this zone? We also wanted to find out if a targeted intervention could improve the knowledge, attitude and practice of pharmacovigilance of health care professionals in the South-South Zone as well as increase the number and quality of adverse drug reaction reports.

The specific objectives of this thesis were:

1. To determine the factors influencing the establishment of pharmacovigilance system in a resource poor setting.
2. To characterise the state of pharmacovigilance in tertiary health care facilities in the South-South zone using pharmacovigilance indicators.
3. To assess knowledge, attitude and practices of healthcare practitioners in the South - South zone regarding Pharmacovigilance.
4. To evaluate the reporting of ADRs in tertiary health care facilities in South-South Nigeria.

After this introduction, the thesis is organised in7 chapters:

In **chapter 1,** we give an overview of Pharmacovigilance in Nigeria, describing the Nigerian pharmacovigilance landscape and governance structure, the challenges and the achievements.

In **chapter 2**, we undertook an assessment of the state of Pharmacovigilance in South-South Nigeria using the WHO Core pharmacovigilance Indicators in order to characterise the state of pharmacovigilance at the level of teaching hospitals.

In **chapter 3,** we described the drug utilisation practices in the South-South zone using the WHO Core drug prescribing indicators.

In **chapter 4**, we evaluated the knowledge, attitude and practice of healthcare professionals regarding pharmacovigilance in South- South Nigeria.

In **chapter 5,** we evaluated the impact of an educational intervention and text message reminders on the knowledge and attitude of health care professionals.

In chapter 6, we described the adverse drug reactions that had been reported to the pharmacovigilance committee in the South-South zone of Nigeria before and after an educational intervention

In **chapter 7,** we reviewed the adverse effects profile of antihypertensive drugs as reported by the patients in a tertiary care clinic in Nigeria.

A general discussion is concluding the thesis.

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CHAPTER 1:

PHARMACOVIGILANCE IN NIGERIA- AN OVERVIEW

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Olowofela A. Fourrier-Reglat A, Isah A. Pharmacovigilance in Nigeria: an Overview. Pharmaceutical Medicine. 2016; 30 (2): 87-94.

The final publication is available at: https://link.springer.com/article/10.1007/s40290-015-0133-3

Pharm Med
DOI 10.1007/s40290-015-0133-3

LEADING ARTICLE

Pharmacovigilance in Nigeria: An Overview

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Abstract Nigeria was admitted into the WHO International Drug Monitoring Programme in 2004. That marked a new era of pharmacovigilance in Nigeria. Nigeria is a large country in sub-Saharan Africa with essentially a homogenous black population of over 170 million people, a significant disease burden (communicable and non-communicable) and consequent medication use. Inevitably, the need for medicine safety is becoming increasingly appreciated by the government, health-care workers and patients. Pharmacovigilance activities in Nigeria are co-ordinated by the National Pharmacovigilance Centre (NPC) situated in the National Agency for Food and Drug Administration and Control (NAFDAC—the drug regulatory agency in Nigeria). NPC serves as a repository for reported adverse drug reactions from health workers and also liaises with other international groups such as the WHO, US Food and Drug Administration and the European Medicines Agency in improving drug safety in Nigeria. Increasing participation of the public in drug safety is also a major thrust of the NPC and the contributions of public-health programmes in this resource-poor setting to pharmacovigilance cannot be overemphasised. The provisions of a unique policy to define the responsibilities of the stakeholders in pharmacovigilance, as well as training of the health-care workers, are a few of the achievements of the agency in charge of pharmacovigilance in Nigeria.

Key Points

Pharmacovigilance is a growing entity in Nigeria, the largest homogenous black population in Sub-Saharan Africa with a morbidity mix resulting in complex medication use.

The profile of adverse reactions and burden is yet to be fully characterised in this resource-poor setting.

The Nigerian National Pharmacovigilance Centre is in charge of pharmacovigilance activities in the country and interacts with the public, health workers, patients, marketing authorisation holders and the WHO and other international agencies.

A stand-alone pharmacovigilance policy has been approved in Nigeria.

1 Introduction

Nigeria is a developing nation in the West African sub-region with a large population of 170 million persons and a myriad of health- and medicine-related problems. The morbidity and mortality related to medication use has not been formally quantified in the country. However, poor

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Published online: 19 January 2016

recognition of the problem is a major contributor to the morbidity and mortality profile associated with medication-related problems. The Nigerian government, in realisation of the need for improved safety of medicines, set up the National Agency for Food and Drug Administration and Control (NAFDAC), the regulatory agency in charge of drug-related matters in Nigeria. The agency was established by the Federal government of Nigeria by promulgation of a military decree 15 of 1993 amended in democratic dispensation to Act Cap N1 LFN in 2004 [1, 2]. It was mandated to control and regulate the manufacture, importation, exportation, distribution, advertisement, sale and use of food, drugs, cosmetics, chemicals, medical devices and all drinks including packaged water [1, 2]. It has many directorates and the Pharmacovigilance/Post-Marketing Surveillance directorate is in charge of pharmacovigilance [3].

Pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" [4]. There has been expansion of the scope from only drugs to other products, such as herbals, blood products, biologicals, medical devices and vaccines [4]. The other related issues in pharmacovigilance worldwide include medication errors, lack of efficacy reports, off-label use of medicines, acute and chronic poisoning, assessment of drug-related mortality, misuse of medicines as well as adverse interactions of medicines [4]. Nigeria is not exempt from these problems. This overview is intended to review pharmacovigilance in Nigeria, with an emphasis on adverse drug reactions (ADRs).

1.1 Adverse Drug Reactions and Other Pharmacovigilance-Related Issues in Nigeria

Nigeria is a country in Africa with a huge homogenous black population. However, there are diversities in ethnic, climatic, regional and the environmental differences which will likely have influences on the ADR profile even within the country population observed, and invariably are likely to differ from that seen in a largely Caucasian population. The burden of ADRs in Nigeria is not known but there have been notable medication-related events that highlighted the need for a more focused direction for pharmacovigilance. These have been quite striking and tragic.

ADRs are defined as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, therapy of disease, or for the modification of physiological function" [5]. There have been reports in the literature of different adverse reactions observed in Nigerians. In 1964, 350 patients had fixed drug eruptions to dapsone, phenolphthalein, sulphonamides and some other medicines, and it was observed that these reactions may have occurred more frequently in black people than in Caucasians [6]. A review by Salako in 1984 outlined some of the adverse reactions attributable to the different antimalarial drugs that had been reported in Nigerians and these included chloroquine-induced pruritus, and Stevens-Johnson syndrome from sulphonamides, among others [7]. Other notable adverse reactions reported in the Nigerian literature include increased frequency of micturition from use of dihydropyridine, acute encephalopathy following oral metronidazole therapy, quinine and halothane inducing parkinsonism, and acute dystonic reactions following use of antipsychotics [8–11]. Adverse reactions were also reported in children [12, 13]. A compilation of the local Individual Case Safety Reports (ICSRs) and health facility reports in 2005 showed that dipyrone may have been responsible for some cases of necrosis of the skin, subcutaneous tissue and muscles (Nicolau syndrome), necessitating its withdrawal in Nigeria [14]. Other compilations in the NAFDAC pharmacovigilance newsletters further highlights various adverse reactions (including serious adverse reactions) to different classes of medicines received at the National Pharmacovigilance Centre (NPC) [15–17]. Furthermore, the ICSRs forwarded to the NPC from inception to date also highlight that there has been an increase in the number of reports over the years, (Fig. 1; Unpublished data, NAFDAC) and anti-infective drugs for systemic use account for >50 % of adverse reactions in the database (Fig. 2; Unpublished data, NAFDAC). The systems most affected (system organ classification) in the database were skin and subcutaneous tissue disorders, nervous disorders, and gastrointestinal disorders (Unpublished data, NAFDAC).

The public-health programmes where medicines are given freely have also contributed to the available data of adverse reactions in Nigeria. Adverse reactions reported

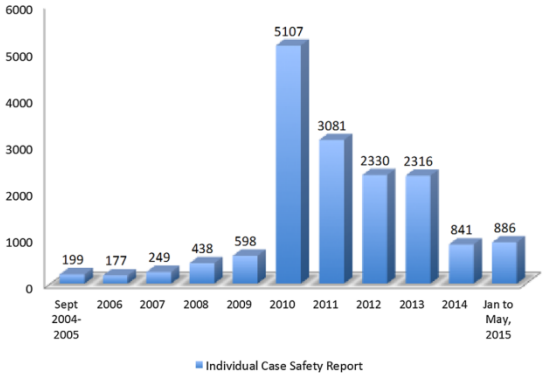

Fig. 1 Number of Individual Case Safety Reports received at the National Pharmacovigilance Centre in Nigeria between September 2004 and May 2015

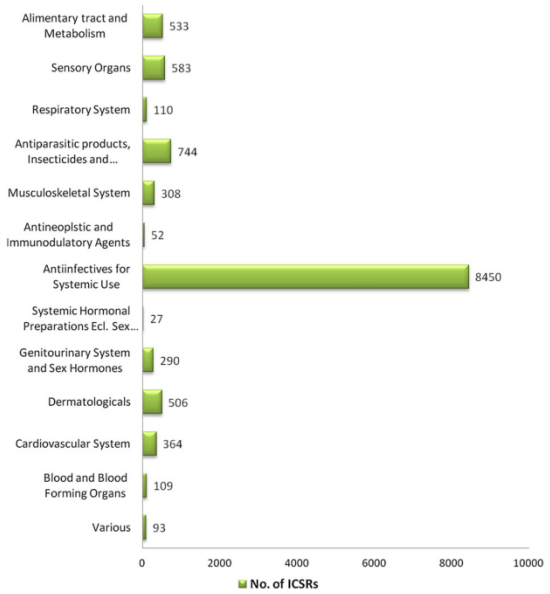

Fig. 2 Number of Individual Case Safety Reports (ICSRs) shown by pharmacological classification (WHO Drug Dictionary) received at the National Pharmacovigilance Centre in Nigeria between September 2004 and May 2015

from an onchocerciasis programme included arthralgia, pruritus and fever seen in patients treated with ivermectin [18, 19]. The HIV and tuberculosis programmes also had reports of mostly dermatological, gastrointestinal and nervous system adverse reactions reported following use of highly active antiretroviral therapy (HAART) medicines and anti-tuberculous agents [20–25]. Generalised body weakness, dizziness and gastrointestinal symptoms were also encountered in the cohort event monitoring of artemisinin-based combination therapy [26]. More public-health programmes sent reports to the NPC from 2010 and this increased the number of reports in the database (Fig. 1).

There is a high use of herbal medicines in the country [27–30] and this has been associated with adverse reactions such as vomiting, dizziness, rashes, diarrhoea and others [30–32]; they have also been found to contain high concentrations of heavy metals [33].

Quality issues have also contributed adversely to the burden of ADRs in Nigeria [34] and this has been seen in large-scale incidents that attracted public outcry. In 1989, poorly compounded chloroquine syrup killed several children at Enugu in South East Nigeria. However, the actual number of cases is not known. Also, in the following year paracetamol was compounded with diethylene glycol, "a coolant", as a solvent, instead of propylene glycol. This toxic mixture resulted in the death of 109 children in Jos and Ibadan [35].

There have been three major episodes of contaminated dextrose infusions with fungi resulting in serious adverse reactions from 2002 to 2004. Also, in 2003 there were reports of substandard epinephrine used during open heart surgery, as well as substandard muscle relaxant and non-sterile infusions [35]. The diethylene glycol incident recurred in 2008 when a teething powder (My pikin®) was again mixed with diethylene glycol; this resulted in over 100 deaths [36].

In Nigeria, the focus of pharmacovigilance has essentially been on ADRs, as well as substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medicinal products. The issue of SSFFC medicines came to the fore in Nigeria when it was revealed that in 1989, about 25 % of products in the Nigerian market were genuine, 25 % were fake medicines and 50 % were inconclusive [37]. Another survey equally showed about 48 % of drugs sampled did not conform to international pharmacopoeia standards [35].

2 The Growth and Organisation of Pharmacovigilance in Nigeria

The Ministry of Health in Nigeria has been involved in trying to improve drug safety since the 1980s, with the sponsorship of some members of staff for training at the Uppsala Monitoring Centre. Major strides in the history of pharmacovigilance in Nigeria was however recorded when the University of Benin Teaching Hospital (UBTH), under the leadership of one of the authors (AOI), set up an adverse reaction monitoring unit in 1989, with the establishment of an ADR registry and drug/poison information centre in 1994 [38]. The unit also set up a reporting scheme that generated enough spontaneous adverse reaction reports to culminate in the setting up of the NPC in 2003 and subsequent admission into the International Drug Monitoring Programme in 2004 with reports obtained from the UBTH. It was granted full membership in 2004 thus becoming the 74th member of the programme [39].

The NPC developed ADR reporting forms, and guidance documents to aid health-care workers and marketing authorisation holders (MAHs) report ADRs properly [1, 40] and also set up training for health-care providers, as well as patent medicine dealers. Due to the increasing recognition of pharmacovigilance in NAFDAC, the pharmacovigilance unit was initially merged with the Food and Drug Information Centre to become the Pharmacovigilance/Food and Drug Information Centre (PVG/FDIC) in 2006 [41], and then upgraded in 2012 to a directorate responsible for pharmacovigilance and post-marketing

surveillance issues [3]. Also in 2006, the National Drug Safety and Advisory Committee (NDSAC) was inaugurated to provide expert advice on issues relevant to pharmacovigilance. Furthermore, in 2013 there was the formal creation of zonal centres in the six geopolitical zones in the country to improve reporting from different parts of the country. The zonal centres are located in tertiary institutions involved in significant pharmacovigilance activities.

2.1 The Governance Structure of the Pharmacovigilance System

Pharmacovigilance in Nigeria at present is being coordinated at the NPC located at the headquarters of NAFDAC in Abuja. The NPC receives individual spontaneous case reports from health-care workers directly, through NAFDAC State Coordinators or through the newly created zonal centres. The zonal centres receive case reports from the states that comprise the zones and forward them to the NPC. They also disseminate information from the NPC to the periphery, carry out training in pharmacovigilance, and enlighten health-care providers on issues relating to pharmacovigilance, as well as paying advocacy visits to stakeholders (Fig. 3).

The NPC also receives mandatory ADR reports from MAHs, in addition to conducting pharmacovigilance inspections of the MAHs, and is responsible for the collection, collation, analysis and evaluation of all ICSRs in the country. The evaluation of the reports is usually done at the NPC and a substantial number, especially those that pose a challenge, are verified by the NDSAC using WHO criteria. These are now managed and forwarded to the WHO Uppsala Monitoring Centre using the VigiFlow™ software and then kept in VigiBase™ (WHO database for ADR reports) to improve signal detection. The NPC acknowledges ICSRs and disseminates information through periodic (quarterly) newsletters to health-care workers. It also works closely with members of NDSAC, which is made up of medical and pharmaceutical experts in related fields. They provide expert advice on current and emerging issues in pharmacovigilance and make appropriate recommendations to the head of NAFDAC regarding drug safety. There is also collaboration with other regulatory agencies such as the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) to enhance the workings of the centre.

In instances where there are safety concerns, appropriate actions are taken, which may range from issuance of advisories (e.g. Dear 'Healthcare Provider' letters, public alerts) to outright withdrawal of the drug.

2.2 Legal Framework for Pharmacovigilance in Nigeria

The NAFDAC Act Cap N1 LFN of 2004 (amended) [2] provides a legal backing for the activities carried out by the NPC. Furthermore, the national drug policy document issued in 1990 (revised in 2005) [42] again highlighted

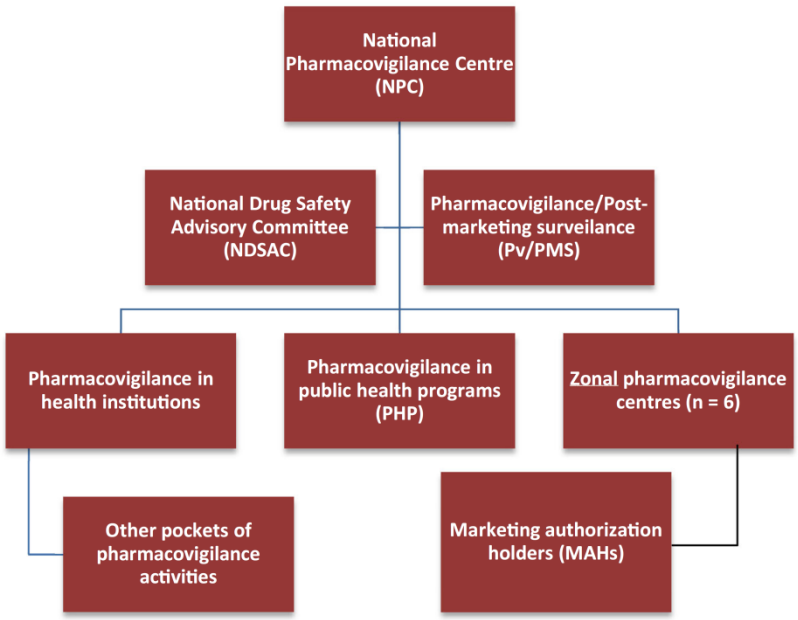

Fig. 3 Schematic diagram showing the operation of the pharmacovigilance system in Nigeria

the drug safety issues. Also, the Nigerian national pharmacovigilance policy and implementation framework serves as the policy document that guides the operations of the system. It was released in 2012 and formally launched in 2013 [43]. The policy is to serve as a tool for the three tiers of government and its partners in the private sector and non-governmental organisations. It provides guidance for the development, implementation, monitoring and evaluation of all aspects of pharmacovigilance. In all it defines the pharmacovigilance system ensuring that the risk–benefit assessments of medicines would ultimately promote the rational and safe use of medicines. It also provides for the creation of zonal centres and the effective operation of pharmacovigilance methods. It outlines the role of the stakeholders in the pharmacovigilance arena including the Ministry of Health, the various tiers of government, the regulatory agency, MAHs, the various cadre of health-care providers and the patient—consumer. At present, the reporting of ADRs is voluntary for health-care workers but mandatory for MAHs.

The policy document also delineates the handling of issues such as reporting of adverse events during clinical trials and public-health programmes, amongst others [43].

3 Achievements and Limitations of the Nigeria Pharmacovigilance System

3.1 Achievements

There has been a lot of activity in the pharmacovigilance arena in Nigeria in recent times. Paramount is the acceptance of the pharmacovigilance policy; the first as a standalone policy document in sub-Saharan Africa and an indication of the government's will to establish pharmacovigilance in the country. The increasing involvement of tertiary institutions due to establishment of the zonal centres and training of the zonal coordinators and other health-care workers is another positive step. Furthermore, the creation of awareness through distribution of guidance documents on pharmacovigilance, ADR reporting forms, training of health-care practitioners in ADR reporting, increased publicity of pharmacovigilance using electronic and print media, and notification of health-care workers through the periodic newsletters are significant activities facilitating the growth of pharmacovigilance in the country.

The NPC has been involved in research activities, and in 2010 carried out a multicentre cohort event monitoring study on antimalarial drugs as a form of active pharmacovigilance [26]; this was to ascertain the tolerability and safety profile of the artemisinin-combination therapy, which is the new standard of care in treating malaria, a highly prevalent disease in Nigeria. There have also been increasing pharmacovigilance activities in other public-health programmes such as antiretroviral and anti-tuberculous medicines. The number of reports in the NPC database has also increased to 16,222 reports between September 2004 and May 2015, although only 11,000 reports have been committed to the WHO database. These reports, as well as reports from international partners, have helped the NPC in sending out appropriate notices such as withdrawal of dipyrone, gentamicin 280/2 mL, and rosiglitazone from the market; warnings against use of unregistered products; medicine recalls; information relating to change of labelling of medicines; and recommendations for risk management activities, among others [44]. The other areas that receive attention at the NPC and form a major part of the thrust of the NPC include the SSFFC medicines, detection of medication errors and reports of lack of effectiveness of medicines [43].

Furthermore, there has been the introduction of an ADR reporting system whereby the public report directly to the NPC through a short messaging system (SMS) named Pharmacovigilance Rapid Alert System for Consumer Reporting (PRASCOR). This allows the public to send a text message to a dedicated number relating the ADR that they have experienced. There would be a response from the NPC to capture the ADR information and ultimately help the patient [45].

3.2 Limitations

Despite the number of years that pharmacovigilance has been established in Nigeria, there are still some challenges within the system. Nigeria is yet to achieve the optimum target of 200 reports per million population recommended by the WHO [46], despite the increased number of reports committed to the WHO database. Poor recognition of ADRs, under-reporting, cumbersome reporting processes of ADRs, and a lack of dedication to pharmacovigilance by institutional heads have been shown to contribute negatively to the low number of reports received by the NPC [47–49]. Institutionalisation of pharmacovigilance in health-care facilities both at the federal and state level is still a main objective of pharmacovigilance in Nigeria, as only a few tertiary hospitals are fully involved in pharmacovigilance. This is an important objective that has been captured in the pharmacovigilance policy; however, implementation is slow. There is much focus on educating health-care workers, and creating awareness to improve reporting.

There are also a limited number of experts in the field of pharmacovigilance, which may have retarded the growth of pharmacovigilance, especially in Nigeria. Thus, there is need for more capacity building in order

to fully integrate pharmacovigilance into the health-care system [50]. The efficient maintenance of the database is also beset by inadequate electricity supply and broadband internet services. In addition, funding to support the infrastructure and the set of pharmacovigilance activities is non-existent or grossly inadequate. There is also insufficient political goodwill towards issues relevant to pharmacovigilance as funding of pharmacovigilance in Nigeria remains largely under the purview of the Federal government. It is hoped that the development of the policy will influence the states and local government councils to take more active participation in pharmacovigilance.

The picture is similar to that found in other African countries as shown in a recent review by Isah et al. [51] where pharmacovigilance and other safety concerns remain underappreciated. They also highlighted a need for increasing awareness for pharmacovigilance. Infrastructural challenges, insufficient experts in the field, and hesitation in ADR reporting are a few of the problems associated with pharmacovigilance in Africa. In the development of pharmacovigilance systems in other parts of Africa, there exist fundamental problems that are profound and similar, notably a lack of political goodwill and poor funding [51].

This trend of low numbers of ADR reports reflects that obtained in other lower and middle-to-low income countries as shown in a study that reviewed spontaneous reports to the WHO ADR database Vigibase™ from 2000 to 2009 [52]. Poor development of the organisation of pharmacovigilance, as well as inadequate resources, are some identifiable problems that may have contributed to such poor reporting rates [50].

As in other pharmacovigilance systems worldwide, problems such as under-recognition, under-reporting, parallel reporting in public-health programmes, fear of possible intellectual property right issues by the researchers, fear of litigation or penalty following reporting are prevalent [53, 54].

4 Future Prospects

There is room for improvement in pharmacovigilance in Nigeria and there is a need to understand the perceptual differences that hinder reporting in Nigeria. Processes that can be developed to further enlighten health-care workers on the need for pharmacovigilance should be put in place. The impact of patient reporting needs to be evaluated and strengthened, and as the burden and profile of ADRs in the Nigerian setting is as yet undetermined, multicentre large-scale studies need to be carried out to properly quantify and put into perspective this all-important area of patient safety. Also of interest is the need to characterise the ADRs related to herbal medicines, which are used extensively by the Nigerian population.

5 Conclusions

A pharmacovigilance system with the basic infrastructure and activities has been established in Nigeria in the last decade. There has been notable growth in the number of reported ICSRs with the establishment of zonal centres and the provision of guidance with a dedicated pharmacovigilance policy. This tempo is likely to be maintained, despite the enormous challenges, if given the necessary support and goodwill by the government.

Acknowledgments We hereby acknowledge the Director General of the National Agency for Food and Drug Administration and Control (NAFDAC) Nigeria, the Head of the Pharmacovigilance and Post-Marketing Surveillance Directorate at NAFDAC as well as Dr. Olubusayo Akinola and other members of staff of NAFDAC for their kind assistance.

Compliance with Ethical Standards

Funding This article was self-sponsored and funded.

Conflict of interest Abimbola Olowofela declares no conflict of interest relating to this article. Annie Fourrier-Réglat declares no conflict of interest relating to this article. Ambrose O. Isah declares no conflict of interest relating to this article.

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CHAPTER 2 :
ASSESSMENT OF THE STATE OF PHARMACOVIGILANCE USING THE WHO CORE PHARMACOVIGILANCE INDICATOR

Chapter 2 Assessment of the state of pharmacovigilance using the WHO core pharmacovigilance indicators

Opadeyi AO, Fourrier-Réglat A. Isah AO**.** Assessment of the state of pharmacovigilance using the WHO core pharmacovigilance indicators. BMC Pharmacology and Toxicology. 2018; 19:27

Final publication available at: https://doi.org/10.1186/s40360-018-0217-2

Opadeyi *et al. BMC Pharmacology and Toxicology* (2018) 19:27
https://doi.org/10.1186/s40360-018-0217-2

BMC Pharmacology and Toxicology

RESEARCH ARTICLE Open Access

Assessment of the state of pharmacovigilance in the South-South zone of Nigeria using WHO pharmacovigilance indicators

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Abstract

Background: WHO pharmacovigilance indicators have been recommended as a useful tool towards improving pharmacovigilance activities. Nigeria with a myriad of medicines related issues is encouraging the growth of pharmacovigilance at peripheral centres. This study evaluated the status of pharmacovigilance in tertiary hospitals in the South-South zone of Nigeria with a view towards improving the pharmacovigilance system in the zone.

Methods: A cross-sectional descriptive survey was conducted in six randomly selected tertiary hospitals in the South-South zone of the country. The data was collected using the WHO core pharmacovigilance indicators. The language of assessment was phrased and adapted in this study for use in a tertiary hospital setting. Data is presented quantitatively and qualitatively.

Results: A total of six hospitals were visited and all institutions had a pharmacovigilance centre, only three could however be described as functional or partially functional. Only one centre had a financial provision for pharmacovigilance activities. Of note was the absence of the national adverse drug reaction reporting form in one of the hospitals. The number of adverse drug reaction reports found in the databases of the centres ranged from none to 26 for the previous year and only one centre had fully committed their reports to the National Pharmacovigilance Centre. There were few documented medicines related admissions ranging from 0.0985/1000 to 1.67/1000 and poor documentation of pharmacovigilance activities characterised all centres.

Conclusion: This study has shown an urgent need to strengthen the pharmacovigilance systems in the South-South zone of Nigeria. Improvement in medical record documentation as well as increased institutionalization of pharmacovigilance may be the first steps to improve pharmacovigilance activities in the tertiary hospitals.

Keywords: Pharmacovigilance, Adverse drug reaction reporting, Nigeria, Tertiary hospitals

Background

Pharmacovigilance in Nigeria commenced in the late 80s and early 90s initially in a tertiary hospital with some preparatory activities at the national level prior to its admission into the WHO program for international drug monitoring (PIDM) in 2004 [1, 2]. It has sustained its activities through active training of healthcare workers, sensitisation campaigns using print and electronic media about medicine safety issues to health care workers and the public [3]. It has also carried out active surveillance through the cohort event monitoring on adverse reactions to antimalarials (artemisinin-based combination therapy) [4]. There has also been the introduction of electronic devices to reduce substandard and falsified medical products which is a major contributor to adverse drug reactions in our setting.

The growth of pharmacovigilance in Nigeria has been propelled by a number of factors including the establishment of the regulatory agency (National Agency for Food

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and Drug Administration and Control – NAFDAC) by Decree 15 of 1993 (as amended) now cited as Act Cap N1 laws of the Federal Republic of Nigeria 2004, the formulation of the Nigerian National Drug Policy in 2005 [5]. This was further clarified by the introduction of the Nigerian pharmacovigilance policy document in 2012 firmly positing drug safety in national discussion [6]. The actualization of some of these goals has recorded significant progress with the formation of the zonal centres to cover the six geo-political zones in the country in 2012 [7].

Pharmacovigilance has a wide scope with increasing product concerns. The main focus in the Nigeria context has been on adverse drug reactions, substandard and falsified medical products [3, 8–10]. Other areas yet to be fully addressed include medication errors [11], lack of effectiveness reports, acute and chronic poisoning [12, 13], assessing drug related mortality as well as abuse and misuse of medicines [3, 9]. The determination of the burden of these various problems has been poor as the major challenge to the growth of pharmacovigilance in Nigeria has been that of under-reporting as seen worldwide [14–16].

Reporting of drug safety concerns by health-workers in Nigeria is voluntary and the reasons for under-reporting are partly due to fear of litigation, poor understanding of the subject matter, feeling that the "known" Adverse Drug Reactions (ADRs) need not be reported, time constraints and cumbersome reporting processes [17–21]. Lack of appropriate structures and deficient processes at the institutional level may also contribute to the poor reporting rate as found in some studies [17, 21–23].

WHO advocates regional centres as an effective way of enhancing pharmacovigilance activities [24] as observed in some areas of the world where this has been found to improve the number and quality of reports [25, 26].

The aims of the creation of the zonal centres was to decentralize the activities of the National Pharmacovigilance Centre (NPC), e.g. distribution of ADR forms and collection of the Individual Case Safety Reports (ICSRs) from reporters and perform preliminary evaluation with prompt reporting, also transmission of acknowledgements and feedback information to the reporters and dissemination of information from the national centre to the patients and health care workers. Furthermore, they were created to monitor the progress of pharmacovigilance activities at institutional levels as well as support the training and capacity building for pharmacovigilance in the areas of their jurisdiction [6]. These measures would further increase awareness about pharmacovigilance and instil a sense of ownership among the stakeholders regarding pharmacovigilance activities as well as bring closer to the reporters a centre close to their practice.

Currently, the assessment of pharmacovigilance had been largely done at the national level using various tools including evaluating the attainment of minimum requirements for a national centre with interviews of focal persons [27], and recently the use of the Indicator based Pharmacovigilance Assessment Tool (IPAT) indicators [28]. The more recent introduction of the WHO pharmacovigilance indicators provides an opportunity to assess pharmacovigilance activities at the national centres [29]. These indicators targeted at the national centres perform self-evaluation and also identify areas that require intervention. This approach may be applicable to zonal centres and its components which feed data to the national centres. It may also be most appropriate to identify problems at sub-national levels requiring attention [30].

The status of the pharmacovigilance system in the tertiary centres is presently unknown as the WHO indicators and related metrics for evaluating these centres have just been recently released [29] and there is little or no data on the effectiveness and functionality of these centres at this time. Furthermore, the involvement of these centres in this self-appraisal will further facilitate their participation in measures to remedy identified deficiencies with a view towards improving the quantity and quality of adverse drug reaction reports and other areas in pharmacovigilance. This study intends to assess the status of pharmacovigilance structure, processes, outcomes and impact in the South–South zone of Nigeria using the newly introduced WHO pharmacovigilance indicators.

Methods

Study setting and design

This study was carried out in the South-South Zone of Nigeria which is located in the coastal region of Nigeria. It comprises six states namely Akwa-Ibom, Bayelsa, Cross Rivers, Delta, Edo and Rivers with a population of 21,014, 655 million persons (Nigeria national census 2006). Health care professionals in all tiers of hospitals in this zone could send their reports either directly or through the zonal pharmacovigilance centre for onward transmission to the national centre. The South-South zonal pharmacovigilance centre is domiciled in the University of Benin Teaching Hospital, a tertiary hospital for research and learning.

In Nigeria, heath care is delivered at three levels: primary, secondary and tertiary. Tertiary care hospitals provide the highest level of care and serve as referral centres for the secondary and primary centres. Furthermore, there are three main types of tertiary centres. Firstly: the teaching hospitals, which provide teaching (to most cadres in the health professions at undergraduate and postgraduate levels for medical, nursing, pharmacy students etc.) as

well as for research and health care services. Secondly: Federal Medical Centres which are mainly for health care services as well as providing residency training in some departments and lastly the specialty hospitals which focuses on particular disease entities of public health importance such as neuro-psychiatric hospitals, orthopaedic hospitals and ophthalmic hospitals among others.

This study was directed at the teaching hospitals because they provide the widest access to all patients with an inclusiveness of all cadres of health care workers. In the South-South zone there are eight teaching hospitals, seven are government owned, and one privately owned.

Eligibility criteria: teaching hospitals were used to ensure inclusiveness of all clinical disciplines and staff complement. All six states in the zone were represented by a teaching hospital. An institutional approval was required from the Chief Medical Director / Management prior to inclusion in the study. The study was subsequently carried out in 6 tertiary health institutions selected through simple random sampling in the various states namely:

- University of Benin Teaching Hospital Benin-City, Edo State, (UBTH).
- Delta State University Teaching Hospital Oghara, Delta State, (DELSUTH).
- Niger Delta University Teaching Hospital Okolobri, Bayelsa State, (NDUTH).
- University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, (UPTH).
- University of Uyo Teaching Hospital, Uyo, Akwa-Ibom State, (UUTH).
- University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH).

Prior to visiting the study sites for data collection, ethical approval was obtained from the research and ethics committee of each of the selected tertiary hospitals. Furthermore, the heads of the institution were contacted for approval and access to the pertinent data. The focal persons in charge of pharmacovigilance in the institution provided answers for the indicator assessments.

Data collection

The data were obtained using a modified WHO data collection form for pharmacovigilance indicators [29] by one of the researchers through interviews of the focal person for pharmacovigilance or the pharmacovigilance committee. The components of this form included *the background information, structural indicators, process indicators, outcome/impact indicators.* The phrasing of the assessment questions was adapted to address the tertiary hospital setting (Additional file 1).

The *background information* collected characteristics of the hospitals: teaching hospital staff strength, i.e. number of post registration health professionals in different categories: doctors, nurses, pharmacists, specialist disposition, average out-patient attendance over the last year, total number of beds in the hospital.

The *structural indicators* assessed the existence of key pharmacovigilance structures, systems and mechanisms in any of the settings studies. It details the basic infrastructure needed to enable good pharmacovigilance activities. It assesses the enabling environment needed for pharmacovigilance activities.

The *process indicators* assessed the degree of pharmacovigilance activities in the various centres. It focussed on the processes that describe the collection, collation, analysis and evaluation of ADR reports. The factors influencing these processes were also considered. These measures were assessed directly or indirectly.

The *outcome/impact indicators* measure the extent of realization of the pharmacovigilance objectives. The hospital records used in assessing the outcome/impact indicators include admission and discharge registers, death registers, International coding of disease registers where available. Other requested details were: the total number of outpatient visits in the previous year, the morbidity and mortality statistics of each institution for the previous year (to include the disease statistics of admitted and deceased persons). Furthermore, to compute the duration of hospital stay, the crude estimates of the duration of admission of patients with serious adverse reactions who were hospitalised was calculated from the adverse drug reaction reports obtained for the previous year.

Data analysis

Analysis was both qualitative and quantitative. All hospitals participating in the study were described according to each indicator. The core Structural indicators are qualitative indicators with categorical data analysed descriptively. The presence or absence of the parameter measured was described for each institution.

Analysis of the core Process and Outcome Indicators are quantitative indicators reflecting rates of reports and actual numbers. They were calculated using frequencies and absolute numbers as dictated by the indicator. The data was analysed with descriptive statistics using Microsoft excel 2007.

Results

All six institutions were visited and the focal Pharmacovigilance persons or committees interviewed following a meeting with the various heads of the institutions. The teaching hospitals in this study are all government owned and serve as referral centres to the primary and

secondary tier hospitals. However, they are of varying sizes in terms of bed and staff complement. The demographic characteristics of the institutions at the commencement of the study late January to mid-March 2016 were as follows (Table 1).

Core structural indicators

Responses were obtained from the interviewed personnel for the assessment questions of the 10 structural indicators for all the institutions studied. Three of the 6 institutions had a standardised functional accommodation for pharmacovigilance activities while 1 had non functional rooms and 2 had none. Only one hospital had regular financial provisions for pharmacovigilance. The secretariat in 4 centres had a full time staff to carry out pharmacovigilance activity while 2 had part time staff. Of note was the availability of an institutionalized ADR reporting form in one of the six centres (DELSUTH) while a centre neither had copies of the national nor local forms available. There were no standard forms available which addressed the subset of assessment questions covering the scope of pharmacovigilance in all of the centers (Table 2).

Core process indicators

The absolute number of ADR reports received among the 6 hospitals in the previous year ranged from 0 to 26, two hospitals had no reports for the previous year 2015. Furthermore, the total number of reports in the local database ranged from 0 to 831. Cohort event monitoring of antimalarials (artemisinin-based combination therapy) was carried out and completed in UBTH in the five years preceding the analysis as a form of active surveillance. There were limited numbers of reports on ADRs, medication errors, lack of therapeutic effectiveness etc. in most of the centers. Documentation of feedback and causality assessment carried out on reports in the centers was equally poor in this study (Table 3).

Core outcome/impact indicators

Unusual reports regarding the development of frequent micturition following use of amlodipine besylate was observed in one of the centers and is being evaluated (Table 4). The number of medicine-related hospital admissions per 1000 admissions ranged from 0.00958/1000 to 1.67/1000 and there were no documentations of medicine related deaths in the death registers in the various hospitals. The documentation of pertinent data was inadequate, rendering calculation of other outcome/impact pharmacovigilance indicators in the institutions difficult (Table 4).

Discussion

This is the first published study evaluating the practice of pharmacovigilance in tertiary hospitals of the South-South zone of Nigeria using the WHO indicators. The study has highlighted the strengths and weaknesses of the pharmacovigilance sub-healthcare system in general.

The study revealed that structures were gradually being put in place and there was a general acceptance of the need for pharmacovigilance in all the institutions visited despite institutional challenges. The availability of the newly developed Nigerian national pharmacovigilance policy in some of the centers is a testament to the will of the Nigerian government to institutionalize patient safety through good pharmacovigilance practice.

It was observed that the UBTH performed better than the other hospitals within the zone, this was ascribed to the activities of the pharmacovigilance team and system that started off in the early 90s [2] and has been largely sustained by the commitment of the pharmacovigilance committee, staff and management. It was also observed that despite DELSUTH and NDUTH being relatively smaller hospitals in terms of bed complement, they still performed better than some larger hospitals. This suggests that interest of the key stakeholders in the pharmacovigilance program is needed to sustain the development of the pharmacovigilance system.

Table 1 Characteristics of the tertiary teaching hospitals in the South-South Zone[a]

Characteristic	UCTH	UUTH	UPTH	NDUTH	DELSUTH	UBTH
Number of beds	610	499	782	148	250	701
Approximate number of health care workers (post registration)	1141	739	1028	253	532	1219
Consultant Clinicians	146	86	179	85	65	200
Doctors	359	124	210	53	150	335
Nurses	580	417	600	105	300	660
Pharmacists	56	19	39	10	17	24
Out-patient attendance in the previous year (2015)	81,624	114,523	114,277	32,906	22,540	179,255
Number of in-patient hospital admissions (2015)	7171	9679	10,145	2548	No data	11,324

[a]*UBTH* University of Benin Teaching Hospital Benin-City, Edo State, *UCTH* University of Calabar Teaching Hospital, Calabar Cross-River State. *UPTH* University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, *UUTH* University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State. *DELSUTH* Delta State University Teaching Hospital Oghara, Delta State, *NDUTH* Niger Delta University Teaching Hospital Okolobri, Bayelsa State

Table 2 Analysis of WHO Core Pharmacovigilance Structural Indicators of the six tertiary hospitals in the South-South zone of Nigeria

Indicator Item	Assessment	UCTH	UUTH	UPTH	NDUTH	DELSUTH	UBTH	Hospitals with positive answers (n)
CST1	Presence of pharmacovigilance centre/department / unit with a standard accommodation.	Yes	No	No	No	Yes	Yes	3
CST2	Availability of a copy of the Nigerian pharmacovigilance policy	Yes	No	No	Yes	Yes	Yes	4
CST3	Presence of Institutional Drug Therapeutic Committee	Yes	No	No	Yes	Yes	Yes	4
CST4	Availability of regular financial provision for the pharmacovigilance Centre.	No	No	No	No	No	Yes	1
CST5	Availability of human resources to carry out functions of Pharmacovigilance Centre.	Yes	Yes	Yes	Yes	Yes	Yes	6
CST6	Availability of standard ADR reporting form in the institution.	Yes	Yes	No	Yes	Yes	Yes	5
	CP6a-e: Availability of relevant fields in standard ADR reporting form for a) medication error, b) counterfeit/ substandard medicines, c) therapeutic ineffectiveness, d) suspected misuse, abuse, dependence on medicines, e) general public.[a]	No	No	No	No	No	No	0
CST7	A process is in place for collection, recording and analysis of ADR reports	Yes	No	No	No	Yes	Yes	3
CST8	Incorporation of pharmacovigilance into the orientation programme curriculum of newly employed health care professionals	No	No	No	No	No	Yes	1
	CST8a: for Medical doctors	No	No	No	No	No	Yes	1
	CST8b: for Dentists	No	No	No	No	No	Yes	1
	CST8c: for Pharmacists	Yes	No	No	Yes	No	Yes	2
	CST8d: for Nurses/Midwives;	No	No	No	No	No	No	0
CST9	Existence of a newsletter/information bulletin/website as a tool for Pharmacovigilance information dissemination	No	No	No	No	No	Yes	1
CST10	Existence of pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety.	Yes	No	No	Yes	Yes	Yes	4

[a]The items in CST6a-e were all considered separately and the answer was found to be No for each item. *UBTH* University of Benin Teaching Hospital Benin-City, Edo State; *UCTH* University of Calabar Teaching Hospital, Calabar Cross-River State; *UPTH* University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State; *UUTH* University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State; *DELSUTH* Delta State University Teaching Hospital Oghara, Delta State; *NDUTH* Niger Delta University Teaching Hospital Okolobri, Bayelsa State; *ADR* Adverse Drug Reaction; WHO World Health Organization

Interestingly, one of the centers (DELSUTH) modified the ADR form showing their own hospital logo and domiciling the ADR form to their setting. This showed the willingness of the centre to improve patient safety through a sense of ownership. The inclusion of health facilities in the Nigerian national pharmacovigilance policy was to increase their participation in the pharmacovigilance activities [6]. The study revealed poor budgeting for pharmacovigilance as only a center (UBTH) had financial provision for pharmacovigilance. This was distinct from the finding in Rwanda using the Indicator based pharmacovigilance assessment tool (IPAT) where the hospitals studied had budgetary allocation for pharmacovigilance [31]. The availability of relevant staff and committees are paramount to the development of pharmacovigilance and the hospitals with developed committees and personnel disposition had slightly better reports. It is important to fund pharmacovigilance as development of active pharmacovigilance programs, provision of training, feedback, information dissemination and maintenance of the centers are useful tools in pharmacovigilance that require adequate finances [32]. Capacity development is required for the growth of pharmacovigilance as shown in the review of three countries where insufficient manpower contributed to poor development of pharmacovigilance [27].

The processes and outcomes were however poor in all the facilities probably due to lack of awareness of measuring indices to monitor and evaluate pharmacovigilance. Again, the pharmacovigilance system in this setting is still in their infancy and the requisite culture to ensure effective operations yet to be established. However, it was noted that a cohort event monitoring of antimalarials (artemisinin-based combination therapy)

Table 3 Analysis of WHO Core Pharmacovigilance Process Indicators of the six tertiary hospitals in the South-South zone of Nigeria

Indicator Item	Assessment questions	UCTH	UUTH	UPTH	NDUTH	DELSUTH	UBTH
CP1	Total number of ADR reports received in the previous year	16	0	0	1	9	26
CP2	Reports (current total number) in the local database	41	1	0	12	12	831
CP3	Percentage of total annual reports acknowledged/issued feedback	0	0	0	0	0	0
CP4	Percentage of total reports subjected to causality assessment in the previous year.	0	0	0	0	0	84.6
CP5	Percentage of total annual reports satisfactorily completed and submitted to the local Pharmacovigilance Centre in the previous year.	18.8	0	0	0	77.8	84.6
CP5a	Percentage of reports committed to National Pharmacovigilance Centre database from the local Pharmacovigilance centre	0	0	0	0	0	100
CP6	Percentage of reports of therapeutic ineffectiveness received i n the previous year	0	0	0	0	0	0
CP7	Percentage of reports on medication errors reported in the previous year	0	0	0	0	0	7.7
CP8	Percentage of registered pharmaceutical industries having a functional Pharmacovigilance system? Not applicable in this study.	Only applicable at the level of National Pharmacovigilance Centre					
CP9	Number of active surveillance activities initiated, ongoing or completed in the last five years	0	0	0	0	0	1

UBTH University of Benin Teaching Hospital Benin-City, Edo State; *UCTH* University of Calabar Teaching Hospital, Calabar Cross-River State; *UPTH* University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State; *UUTH* University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State; *DELSUTH* Delta State University Teaching Hospital Oghara, Delta State; *NDUTH* Niger Delta University Teaching Hospital Okolobri, Bayelsa State; *ADR* Adverse Drug Reaction; *WHO* World Health Organization

was conducted in UBTH as a part of a national program. This active surveillance of medicines used in a disease of public health importance is useful in obtaining better insights into the safety and tolerability pattern in our setting [4]. The need for the indicators could also be seen in a review of three national centers India, Uganda and South Africa using the WHO minimum requirements for a functional pharmacovigilance system by Maigetter et al. [27] which suggested a more efficient and systematic monitoring for pharmacovigilance system. An awareness of regular pharmacovigilance evaluations with pharmacovigilance indicators would translate to better pharmacovigilance processes and outcomes.

Table 4 Analysis of WHO Core Outcome Pharmacovigilance Indicators in six tertiary hospitals in South-South zone of Nigeria[a]

Indicator Item	Assessment questions	UCTH	UUTH	UPTH	NDUTH	DELSUTH	UBTH
CO1	Number of signals generated in the last 5 years	0	0	0	0	0	1[b]
CO2	Number of regulatory notifications issued in the last year	0	0	0	0	0	0
CO3	Number of medicine-related hospital admissions per 1000 admissions[a]	1.67	1.65	0.0985	0.3924	No data	0.97
CO4	Number of medicine-related deaths per 1000 persons served by the hospital per year	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data
CO5	Number of medicine-related deaths per 100,000 persons in the population	Only applicable at the level of National Pharmacovigilance Centre					
CO6	Average cost (US$) of treatment of medicine-related illness	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data
CO7	Average duration (Days) of medicine-related extension of hospital stay	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data	5.86 days
CO8	Average cost (US$) of medicine-related hospitalization.	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data	Inadequate data

[a]Calculated according to data from Table 1, [b] Frequent micturition following use of amlodipine besylate is being evaluated in the centre
UBTH University of Benin Teaching Hospital Benin-City, Edo State; *UCTH* University of Calabar Teaching Hospital, Calabar Cross-River State, *UPTH* University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State; *UUTH* University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State; *DELSUTH* Delta State University Teaching Hospital Oghara, Delta State; *NDUTH* Niger Delta University Teaching Hospital Okolobri, Bayelsa State; *ADR* Adverse Drug Reaction

The poor record keeping in all the facilities also made computations of the process and outcomes indicators difficult to achieve. The documentation of medicine related events especially adverse drug reactions were equally poor in this study, this contributed to lack of data even in hospitals where the international coding of diseases was been done. This is not different from what has been reported in other studies about under-recognition of adverse drug reactions and drug related events [33, 34]. It is imperative to inculcate a more articulate approach to routine data gathering and documentation into the healthcare system. Furthermore, planned prospective data collection processes should be put in place to enable evaluation of the outcomes and impact of pharmacovigilance activities.

In the utilization of the WHO pharmacovigilance indicators, it is evident that the scope of reportable incidents by the facilities have been broadened and it is hoped that with the implementation framework of the Nigerian national pharmacovigilance policy, there would be a wider dissemination of the roles that tertiary hospitals are to play in the promotion of pharmacovigilance. The WHO pharmacovigilance indicators would be useful in assessing other tertiary hospitals as it would enable the hospital management develop a strategy towards improving patient safety through pharmacovigilance. It may also help identify areas that need urgent intervention or modification in the health information system management of the tertiary hospitals especially since it is recommended that the indicators be reapplied as needed in the facilities.

Limitations

The WHO indicators have proven to be quite useful in this assessment. However, absence of trained pharmacovigilance personnel hindered the provision of results for the pharmacovigilance process indicators in the centers. Of note is the limitation of the structural pharmacovigilance indicators to fully capture the functionality of the pharmacovigilance system. Furthermore, the overall poor documentation in all centers limited the derivation of the indicators. Again the derivation of the outcome/impact indicator required in-depth survey which young pharmacovigilance systems are unable to execute. There might be a need to develop a scoring system to quantify the indices thus highlighting the deficiencies in numerical terms.

Conclusion

This study has shown an urgent need to strengthen the pharmacovigilance systems in the South-South zone of Nigeria. The WHO pharmacovigilance indicators have been proven to be helpful in assessing the pharmacovigilance system in the zone. Improvement in medical record documentation as well as increased institutionalization of pharmacovigilance may be the first steps to improve pharmacovigilance activities in the tertiary hospitals.

Additional file

Additional file 1: Assessment of the state of Pharmacovigilance in the South-South Zone of Nigeria using WHO Pharmacovigilance indicators. WHO Core Pharmacovigilance Indicators including changes made to phrasing of the assessment questions. (PDF 347 kb)

Abbreviations

ADR: Adverse drug reaction; DELSUTH: Delta State University Teaching Hospital Oghara, Delta State; ICSR: Individual case safety report; IPAT: Indicator based Pharmacovigilance Assessment Tool; NAFDAC: National Agency for Food, Drugs Administration and Control, Nigeria; NDUTH: Niger Delta University Teaching Hospital Okolobri, Bayelsa State; NPC: National Pharmacovigilance Centre; UBTH: University of Benin Teaching Hospital Benin-City, Edo State; UCTH: University of Calabar Teaching Hospital, Calabar Cross-River State; UPTH: University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State; UUTH: University of Uyo Teaching Hospital, Uyo, Akwa-Ibom State; WHO: World Health Organization

Acknowledgements

The authors thank the Chief Medical Directors of the various institutions visited as well as the members of the pharmacovigilance committees, units and staff of the hospitals. We are also grateful to the Director General of the National Agency for Food Drugs Administration and Control (NAFDAC) HQ, Abuja and the South – South Zonal Staff for their kind assistance in carrying out this work.

Funding

The study was self funded.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AOO conceptualised the study, modified the data collection tool, collected and analysed data and wrote the initial manuscript. AFR reviewed the protocol, the data collection tool, analysed the data and revised the manuscript. AOI was part of the technical team that drafted the WHO Pharmacovigilance indicators, conceptualised the study, reviewed the study protocol, analysed the data collected and also revised the manuscript. All authors revised and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics and research committees of all participating institutions: Delta State University Teaching Hospital Oghara: DELSUTH/HREC/2015/024, Niger Delta University Teaching Hospital Okolobri,: NDUTH/REC/0005/2015, University of Benin Teaching Hospital Benin-City: UBTH:ADM/E22/2/VOL.VII/1245, University of Calabar Teaching Hospital, Calabar: UCTH/HREC/33/360, University of Port Harcourt Teaching Hospital, Port Harcourt: UPTH/ADM/90/S.II/VOL.X/668 and University of Uyo Teaching Hospital, Uyo: UUTH/AD/S/96/VOL.XIV/357. The heads of the institutions equally gave approval for participation and access to pertinent publicly accessible data; including instructions to the person(s) in charge of pharmacovigilance at the various institutions who then gave verbal consent as approved by the ethics committees. All ethical considerations were duly observed.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 19 January 2018 Accepted: 22 May 2018
Published online: 31 May 2018

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Additional File I
Assessment of the state of Pharmacovigilance in the South-South Zone of Nigeria using WHO Pharmacovigilance indicators.

Abimbola O. Opadeyi,[1,2] Annie Fourrier-Réglat [3,4,5] Ambrose O. Isah,[1,2,6]

WHO Core Pharmacovigilance Indicators including changes made to phrasing of the assessment questions.

#	Core Structural Indicators - Assessment questions	Changes made to assessment questions for Core Structural Indicators (as applicable)
CST1	Is there a Pharmacovigilance Centre / Department / Unit with a standard accommodation?	No changes
CST2	Is there a statutory provision (national policy, legislation) for Pharmacovigilance?	Do you have the national pharmacovigilance policy document?
CST3	Is there a Drug Regulatory Authority/Agency?	Is there Drug Therapeutic Committee in the hospital?.
(CST4	Is there any regular financial provision (e.g. statutory budget) for the Pharmacovigilance centre?	No changes
CST5	Has the Pharmacovigilance Centre human resources to carry out its functions properly?	No changes.
CST6	Is there a standard ADR reporting form in the hospital?	No changes
	CST6a: Are there relevant fields in the standard ADR form to report suspected medication errors?	No changes.
	CST6b: Are there relevant fields in the standard ADR form to report suspected counterfeit / substandard medicines?	No changes.
	CST6c: Are there relevant fields in the standard ADR form to report therapeutic ineffectiveness?	No changes.
	CST6d: Are there relevant fields in the standard ADR form to report suspected misuse, abuse and/or dependence on medicines?	No changes.

	CST6e: Is there a standard ADR reporting form for general public?	No changes
CST7	Is there a process in place for collection, recording and analysis of ADR reports?	No changes.
CST8	Is Pharmacovigilance incorporated into the national curriculum of the various health care professions?	Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed health professionals
	CST8a: Is Pharmacovigilance incorporated into the national curriculum of Medical doctors?	- Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed Doctors?
	CST8b: Is Pharmacovigilance incorporated into the national curriculum of Dentists?	Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed Dentists?
	CST8c: Is Pharmacovigilance incorporated into the national curriculum of Pharmacists?	Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed Pharmacists?
	CST8d: Is Pharmacovigilance incorporated into the national curriculum of Nurses/Midwives?	Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed Nurses/Midwives?
	CST8e: Is Pharmacovigilance incorporated into the national curriculum of others-*to be specified*?	Is pharmacovigilance incorporated into the orientation programme curriculum of newly employed others?
CST9	Is there a newsletter/information bulletin/website (a tool for Pharmacovigilance information dissemination?)	No changes
CST10	Is there a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety?	No changes

	Core Process Indicators - Assessment questions	Changes made to assessment questions for core process indicators (as applicable)
CP1	What is the total number of ADR reports received in the previous year?	No changes
	CP1a: What is the total number of ADR reports received in the previous year per 100,000 persons in population?	
CP2	How many reports are (current total number) in the national/regional/local database?	How many reports are in the local database?
CP3	What is the percentage of total annual reports acknowledged/ issued feedback?	No changes
CP4	What is the percentage of total reports subjected to causality assessment in the year?	No changes
CP5	What is the percentage of total annual reports satisfactorily completed and submitted to the National Pharmacovigilance Centre in the previous year?	What is the percentage of total annual reports satisfactorily completed and submitted to the Local Pharmacovigilance Centre in the previous year?
	CP5a: Out of the reports satisfactorily completed and submitted to the National PV Centre, what is the percentage of reports committed to WHO database?	Out of the reports satisfactorily completed and submitted to the Local PV Centre, what is the percentage of reports committed to National PV Centre?
CP6	What is the percentage of reports of therapeutic ineffectiveness received in the previous year?	No changes
CP7	What is the percentage of reports on medication errors reported in the previous year?	No changes
CP8	What is the percentage of registered pharmaceutical industries having a functional Pharmacovigilance system?	Not applicable at this level.
CP9	How many active surveillance activities are or were initiated, ongoing or completed the last five years?	No changes

#	**Outcome/Impact Indicators - Assessment questions**	**Changes made to Outcome/Impact indicators assessment questions**
CO1	How many signals were generated in the last 5 years by the Pharmacovigilance Centre?	No changes
CO2	How many regulatory actions were taken in the preceding year consequent on National Pharmacovigilance activities?	How many regulatory notifications were received from the National PV Centre and how many were disseminated to the health care professionals.
	CO2a: how many Product Label changes (variation)?	Follow on from CO2
	CO2b: how many safety warnings on medicines to: (CO2bi) health professionals (CO2bii) general public?	Follow on as for CO2: (i) and (ii)
	CO2c: how many withdrawals of medicines?	No changes
	CO2d: how many other restrictions in use of medicines?	No changes
CO3	What is the number of medicine-related hospital admissions per 1,000 admissions?	No Changes
CO4	What is the number of medicine-related deaths per 1,000 persons served by the hospital per year?	No changes
CO5	What is the number of medicine-related deaths per 100,000 persons in the population?	Not applicable at the institutional level
CO6	What is the average cost (US$) of treatment of medicine-related illness?	Omitted in this study as it would require a cost of illness study as suggested by the indicator manual.
CO7	What is the average duration (Days) of medicine-related extension of hospital stay?	No changes.
CO8	What is the average cost (US$) of medicine-related hospitalization?	No changes

CHAPTER 3:

DRUG UTILISATION PATTERN IN SOUTH- SOUTH NIGERIA USING THE WHO CORE DRUG PRESCRIBING INDICATORS

Chapter 3 **Drug utilisation pattern in South- South Nigeria using the WHO Core Drug prescribing indicators**.

Opadeyi AO, Fourrier-Réglat A, Isah AO. Drug utilisation pattern in South- South Nigeria using the WHO Core Drug prescribing indicators

Submitted to African Journal of Medicine and Medical Sciences, December 2018

Abstract

Background: The WHO core drug prescribing indicators has been shown to be useful in understanding drug use patterns and determining the extent of irrational use of medicines in different settings.
Objective: The aim of this study was to evaluate the prescription pattern using the WHO core drug prescribing indicators in the outpatient departments of teaching hospitals in the South-South zone of Nigeria.
Methods: Filled patients' prescriptions sheets from January 2015 to December 2015 were accessed from the records using systematic random sampling method and entered into a data collection sheets. They were evaluated using the WHO core drug prescribing indicators.
Results: Six teaching hospitals were randomly selected and included into the study with a total of 1437 patient encounters and 4635 medicinal products prescribed in 2015. The average number of medicines per patient prescribed was 3.3 (range 1-9). The proportion of medicinal products prescribed with a generic name was 42.5% and the percentage of medicines in the essential medicines list (EML) was 73.5%. The percentage of encounters that included an antibiotic agent was 22.5% and the percentage that included an injection was 6.5%. The most prescribed medicine was paracetamol (25.5%) closely followed by diclofenac (16%).The most prescribed injectable medicine was artemether.
Conclusion and relevance: This study showed good prescribing indices regarding injections and antibiotics but a higher index of polypharmacy, poor utilisation of the EML and lack of adherence regarding generic prescribing compared with previously obtained regional recommended optimal values. It is important to identify safety concerns regarding the commonly used medicines in our environment.
Key words: WHO core prescribing indicators, drug prescribing, rational drug use, teaching hospitals, prescription pattern, Nigeria.

Introduction

Irrational use of medicines is a major factor in the development of adverse drug reactions (ADRs)[1]. It may serve as a major area for intervention in the prevention of ADRs which to a significant extent can be a consequence of irrational use. The broadened scope of pharmacovigilance includes acknowledgement of the contributions of medication errors, misuse and abuse of medicines, poisoning and even more recently the development of antimicrobial resistance[2,3]. It is imperative to examine the use of medicines in order to improve drug safety.

Treatment of diseases should follow Standard Treatment Guidelines (STG) and rational pharmacotherapy. However, it has been shown that poor prescribing practices, poor knowledge of the pharmacology of medicines, lack of awareness of availability of the STGs and of the medicines in the Essential Medicines List (EML), unavailability of the STG and EML are a few of the factors limiting rational pharmacotherapy[4–6].

Drug utilisation studies are usually conducted to review the rational use of medicines in any setting. This could be done on a country wide basis, across regions or in facilities; these studies could be carried out either retrospectively or prospectively using well established registries or databases[7]. In a resource constrained setting like Nigeria, such databases do not exist or are in the elementary forms in most parts of the country. The WHO/International Network of Rational Use of Drugs (INRUD) had advocated a simple means of reviewing drug utilisation of medicines in low resource setting through the application of core drug use prescribing indicators[8]. The indicators allow for comparisons between facilities, regions and countries. They also help hospitals in performing self audits[8]. These evaluations are best carried out periodically to allow for prompt intervention as needed. To conduct a medicine utilization study, associating the medicines with diagnosis would have yielded much better data to enable proper pharmacoepidemiological assessment but there is poor documentation of data in this environment regarding drug use patterns relating to diagnosis and disease patterns. Prescriptions and pharmacy bulk purchase data are all that may be readily available to review the utilization of medicines in Nigeria as the regulations state that these should be retained for some time. Therefore, using the WHO core prescribing indicators are appropriate for use in this setting[8]. Earlier studies in Nigeria, have reported analgesics, antibiotics, multivitamins and antihypertensives as the common medicines in use in Nigeria[9,10] reflecting the health burden seen in a developing world setting.

To enable for appropriate monitoring and comparison, reference values had been established based on a morbidity mix found in the outpatient setting of healthcare facilities in Nigeria[11]. Studies carried out in the setting have highlighted the high prescribing of medicines with the values for the number of medicines, injections exceeding the reference values[12,13].

Most of the earlier studies were carried out in different settings including primary health care centers[9,14,15]. It is expected that general outpatient department of teaching hospitals which are centres of learning should have better prescribing practices. This study was therefore directed at teaching hospitals in a geo-political area in order to determine the compliance with the reference values and profile of drug prescribing practices in their general out-patient departments. This is to enable identification of areas requiring targeted intervention and generally improve patient safety.

Methods

Setting: This study was carried out in six teaching hospitals in the South-South geo-political zone of Nigeria which is located in the coastal region of Nigeria and home to about 21 million residents (National census 2006). The teaching hospitals are centres of teaching, research, clinical services and cater for a wide variety of patients. The government owned randomly selected teaching hospitals included in the study are as follows University of Benin Teaching Hospital Benin-City, Edo State, (UBTH); Delta State University Teaching Hospital Oghara, Delta State (DELSUTH); Niger Delta University Teaching Hospital Okolobri, Bayelsa State, (NDUTH); University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, (UPTH); University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State (UUTH) and University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH)). The hospitals were randomly selected using a table of random numbers. The bed complement ranged from 148 to 701 beds per hospital as at 2015. A retrospective evaluation of prescriptions from the out-patient departments was carried out using the WHO core prescribing indicators in all the centres.

Study population: Prescription sheets of patients who attended the general out-patient clinic during the year 2015 (January to December 2015) were obtained from the hospital pharmacy. The general out-patient department in teaching hospitals attend to various patients in different age groups and therefore have a general morbidity mix pattern. Prescription sheets of patients who visited the other specialist clinics were excluded from this study.

Sample size determination: The WHO/INRUD core drug prescribing indicators manual were used to determine the number of cases to be sampled in each centre. The recommendations dictate that to review prescribing indices, a minimum of 600 prescriptions be sampled from all centres. To improve the reliability of these estimates, a minimum of 1200 prescriptions was overall sampled from the six institutions.

Data collection and analysis

Using the WHO core drug use indicators recommendations to ensure reliability, prescriptions of patients who had visited the pharmacy department after attending the general outpatient department clinic with a varied morbidity mix in the year 2015 were selected from the pharmacy records using a systematic random sampling method. Prescriptions for the whole year were included in the sampling frame to avoid seasonal bias. A minimum of 200 prescriptions were selected per year over the 12 months. Only completed prescriptions were included; the medicine, formulation, and route were also recorded. The generic names when unavailable were determined using standard formularies. All medicines were classified using the Anatomical Therapeutic Chemical (ATC) classification system level 2 [16].The Nigerian national Essential Medicines List (EML) 5th Edition 2010 [17] was used to determine the medicines prescribed from the EML as this was the latest list prior to the study period. The EML was also used to determine which medicines were to be counted as generics. All fixed dose combination (FDC) medicines were counted as one as recommended, also medicines such as metronidazole was regarded as antibiotics in this study due to their use in the context. The WHO prescribing indicators were used to assess rational use with the reference values previously determined [11].

One of the authors (AOO) as well as a research assistant (trained prior to commencement of study) collected the retrospective data using prescription sheets. All data was entered

into Microsoft excel and later analyzed using SPSS version 21 and represented as frequencies, means, standard deviation and percentages. Inferential statistics using ANOVA and chi square were calculated appropriately.

Ethical considerations

Ethical approval was sought and obtained from the ethics and research committees of all the participating institutions. Institutional approval for the study was obtained from the Hospital Head and Management. The patients' details on the prescriptions were coded and anonymised as appropriate and not shared with a third party. All other ethical considerations were met.

Results

A total of six teaching hospitals were included in the study. The number of beds ranged from 148 to 782 and average overall out-patient attendance in 2015was about 91,000 patients (including specialist clinics) are described in table 1.

Using the WHO prescribing indicators, a total of 1437 patient encounters were assessed in this study, with 434 males, 591females and 412 with no sex documented. There were also more adults 991(69%) than children 336 (23.4%); age was not specified in 110 encounters (7.6%).

A total of 4635 medicinal products were prescribed over the study period and the average number (SD) of medicines prescribed were 3.3 (1.7) and this ranged from 1-9 medicines. Table 1.

There was a statistically significant difference between the mean number of medicines prescribed in each hospital as determined by one-way ANOVA (F (5, 1431) = 32.15, p = <0.001). A Tukey post hoc analysis revealed that mean number of medicines was significantly lower in UCTH (2.35 ± 1.3, p = <0.001) compared with the other hospitals while no significant difference existed between UBTH and UUTH but there was a significant difference compared to the other hospitals (DELSUTH, NDUTH and UPTH).

The percentage of generic drugs prescribing was 42.5% overall with a range of 37.3% to 49.4% in the institutions and UUTH being the most adherent with 49.4%, this was also statistically significant ($\chi 2 = 40.1$, $p<0.001$). The percentage of encounters with antibiotics was 22.5% (13.4% to 35%) and UPTH had the largest number of encounters that included an antibiotic, this was also statistically significant ($\chi 2 = 42.2$, $p<0.001$). The percentage of injection prescribed was 6.7% (3.7% to 14.4%). There was a statistically significant difference between the hospitals as well. ($\chi 2 = 29.4$, $p<0.001$). The proportion of medicines prescribed from the EML was 73.5% and this was significant between centres at ($\chi^2 = 39.5$, $p<0.001$). Table 1.

Table 1: Characteristics and summary of the WHO Core prescribing indicators of six teaching hospitals in the South-South Zone of Nigeria from January to December 2015.

Characteristic	UCTH	UUTH	UPTH	NDUTH	DELSUTH	UBTH	Total	P value	WHO optimal values
Number of beds	610	499	782	148	250	701			
Out-patient attendance in (2015)	81,624	114,523	114,277	32,906	22,540	179,255			
Total number of encounters	216	236	223	299	262	201	**1437**		
Total number of medicinal products	502	956	696	900	822	759	**4635**		
Average number of medicine	**2.4**	4.0	3.2	3.1	3.2	3.8	**3.3**	**<0.001[a]**	**1.6-1.8**
Range	1-7	1-9	1-8	1-8	1-9	1-9	**1-9**		
Percentage of medicines prescribed by generic name	**37.3**	49.4	37.4	40	46.4	40.6	**42.5**	**<0.001[a]**	**100%**
Percentage of encounters with antibiotics	27.8	14.9	**35.0**	24.1	19.8	13.4	**22.5**	**<0.001[a]**	**20.0-26.8%**
Percentage of encounters with injections	6.5	3.0	6.3	3.7	8.0	**14.4**	**6.7**	**<0.001[a]**	**13.4-24.1**
Percentage of medicines in the National EML (5th Ed)	76.1	**66.4**	78.0	79.7	77.9	72.3	**73.5**	**<0.001[a]**	**100%**

Abbreviations: ***UBTH****-.University of Benin Teaching Hospital Benin-City, Edo State,* ***UCTH*** *-University of Calabar Teaching Hospital, Calabar Cross-River State.****UPTH*** *-University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State,* ***UUTH*** *- University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State.* ***DELSUTH-*** *Delta State University Teaching Hospital Oghara, Delta State,* ***NDUTH-*** *Niger Delta University Teaching Hospital Okolobri, Bayelsa State.****EML:*** *Essential Medicines List .[a] significant values*

Profile of prescribed medicinal products

The twenty (20) most prescribed classes of medicines using the ATC classifications levels 2 are as shown in Table 2. Antibacterial (16.9%) being the most prescribed class and they were mostly for systemic use (96.2%). There were no prescriptions for antiviral agents in this study. Medicines acting on the cardiovascular system (antihypertensive agents and diuretics) were also commonly prescribed.

Table 2: Most prescribed medicine classes using the Anatomic Therapeutic Chemical classification (ATC) Levels 2 in the general out-patient departments of six teaching hospitals in the South- South Zone of Nigeria

Medicinal classes (ATC Level 2)	Number of prescriptions n=4635	Proportion of total prescriptions (%)
Antibacterials (systemic use and topical)	781	16.9
Vitamins	453	9.8
Analgesics	405	8.7
Antiprotozoals (Antimalarials)	368	8.0
Anti-inflammatory and antirheumatic products	313	6.8
Drugs for acid related disorders(Proton pump inhibitors + Combinations and complexes of aluminium, calcium and magnesium compounds)	212	4.6
Agents acting on the renin-angiotensin system,	210	4.5
Calcium channel blockers	163	3.5
Drugs used in Diabetes	152	3.4
Mineral supplement	145	3.1
Anti-anaemic preparations	144	3.1
Antithrombotic agents	135	2.9
Diuretics	133	2.9
Psycholeptics (Benzodiazepine derivatives)	98	2.1
Antiepileptics	90	1.9
Muscle relaxants	77	1.7
Antihistamine for systemic use	68	1.5
Cough and cold preparations	45	1.0
Antihelminthics	42	0.9
Psychoanaleptics	41	0.9

On further evaluation, of the 4635 prescribed medicinal products, the most prescribed medicine from reviewed prescriptions was paracetamol (8.0%) closely followed by diclofenac (4.3%). Others were vitamins in different forms. The most prescribed antibiotic was amoxicillin/clavulanic acid (2.9%), the most prescribed antimalarial was artemether-lumenfantrine (4%) and the most prescribed antihypertensives were amlodipine (3%) and lisinopril (1.7%). Table 3 describes the 20 most prescribed medicines in the zone. The most prescribed injectable medicine was intramuscular artemether 25.5% followed by paracetamol (16%), and these were mostly from DELSUTH and UBTH (Table 4).

Table 3: Twenty most prescribed medicines in the general out-patient departments of six teaching hospitals in the South- South Zone of Nigeria

Medicine	Total number (n)	Proportion (%)
Paracetamol	370	8.0
Diclofenac	199	4.3
Ascorbic Acid	190	4.1
Artemether/Lumenfantrine	186	4.0
Multivitamin/Vitamin B complex	174	3.8
Amlodipine	140	3.0
Amoxicillin/Clavulanic Acid	136	2.9
Metronidazole	117	2.5
Cefuroxime axetil	92	1.9
Amoxicillin	90	1.9
Ciprofloxacin	88	1.9
Omeprazole	87	1.8
Lisinopril	82	1.7
Acetylsalicyclic acid(75mg strength)	80	1.7
Metformin	71	1.5
Hydrochlorothiazide	69	1.5
Bromazepam	64	1.4
Aluminium Hydroxide/Magnesium Hydroxide	58	1.2
Clopidogrel	56	1.2
Tramadol	55	1.2

Table 4: List of injectable medicines in the general out-patient departments of six teaching hospitals in the South- South Zone of Nigeria

	DELSUTH (n)	NDUTH (n)	UBTH (n)	UCTH (n)	UPTH (n)	UUTH (n)	Total (%)
Artemether	8		14	1		1	24 (25.5)
Paracetamol	3		10		2		15 (16)
Ceftriaxone		2		4	6	1	13 (13.8)
Artesunate	1	2				1	4 (4.3)
Promethazine		1	3				4 (4.3)
Furosemide				2	1	1	4 (4.3)
Tetanus toxoid	3					1	4 (4.3)
Ciprofloxacin		2		1			3 (3.2)
Pentazocine			1	2			3 (3.2)
Diclofenac	2						2 (2.1)
Normal saline	1			1			2 (2.1)
Cefuroxime		1			1		2 (2.1)
Gentamicin		1				1	2 (2.1)
Hydrocortisone		1			1		2 (2.1)
Diazepam			1			1	2 (2.1)
Iron Sucrose	1						1 (1.1)
Pethidine	1						1 (1.1)
Ceftazidime	1						1 (1.1)
Arteether		1					1 (1.1)
Calcium gluconate				1			1 (1.1)
Vitamin B1				1			1 (1.1)
Ringers lactate				1			1 (1.1)
Metronidazole					1		1 (1.1)
Phenobarbitone					1		1 (1.1)
Total	21	11	29	13	13	7	94

Abbreviations: UBTH*-.University of Benin Teaching Hospital Benin-City, Edo State,* ***UCTH*** *-University of Calabar Teaching Hospital, Calabar Cross-River State.****UPTH*** *- University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State,* ***UUTH*** *- University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State.* ***DELSUTH-*** *Delta State University Teaching Hospital Oghara, Delta State,* ***NDUTH-*** *Niger Delta University Teaching Hospital Okolobri, Bayelsa State*

Discussion

This study on the assessment of utilization of medicines in the South –South zone of Nigeria using the WHO core prescribing indicators is the first to be conducted in teaching hospitals across a geo-political zone in Nigeria and it has shown that irrational prescribing practices are prevalent in the region with a high number of medicines per prescription, poor prescribing using brand names and sub-optimal use of the EML. There appears to be some modest improvement compared with previous studies especially regarding use of antibiotics and injections[9,14].

There were more adults in this study as shown by the age distribution in this study and more identified females than males consistent with the clientele seen in the clinics. A significant number of patients did not document their age and gender. The average number of medicines prescribed per encounter was 3.3, which is slightly lower than values in earlier studies but exceeds the existing reference values (1.6 to 1.8) set almost 2 decades ago in two of the states in the same South-South zone[11]. Other studies that have been carried out in similar settings in Nigeria[18,19] since the baseline studies have recorded initial higher mean values than what was observed in this study while some others recorded lower mean values of about 3 per prescription[20]. These values are still quite suboptimal considering that the institutions are tertiary care hospitals with high quality staff. The lack of diagnostic facilities and symptomatic treatment mindset of prescribers may be responsible for the polypharmacy still observed in this study, 20 years after one of the earliest studies in the same geographical area[9]. In another developing country, the mean number of medicine per prescription is lower than what obtained in this study[21]. Furthermore, this also suggests that various interventional strategies to reduce the burden of drug related events may be needed since polypharmacy is rife in the zone and it contributes to drug related events and increased cost of treatment [1].

The study showed there was poor adherence to guidelines that medicines should be prescribed with their generic names as only 42.5% of all medicinal products were prescribed in the generic format. This may be due to undue influences of poor drug promotion practices in the zone[22]. This also increases the risk of medication errors as it has been shown that look or sound alike drugs may lead to medication errors[23]. This was also seen in the previous studies in the area[9,14].

Antibiotic over utilization in non-infective conditions is a leading cause of antibiotics resistance and this has been described as a marginalized area in pharmacovigilance[3]. Accordingly, it is suggested that antibiotics usage should be evaluated in any drug use indicator study[8]. The study showed that there was good adherence with the recommended optimal values of 20 to 26.8% of encounters including an antibiotic as only 22.5% of the encounters in this study included an antibiotic. This is very encouraging especially when compared with earlier studies in some states in the zone where antibiotics use had exceeded optimal values[9,12,14]. However, most of these studies were conducted in primary care centres and private hospitals. Other in-country studies also reported a high use of antibiotics [24,25] but studies from other developing countries show lower usage of antibiotics[26]. The result from this study could be due to previous trainings and education of the physicians on the need to prescribe antibiotics only when needed. Although one of the institutions still showed poor indices of antibiotics over-prescribing, it is believed that this can be remedied with adequate training and other intervention strategies.

All centres displayed good injections safety practices, which is not unexpected considering the country had recently witnessed a surge in hemorrhagic viral diseases and other infectious diseases such as HIV/AIDS, Hepatitis B that are transmissible via blood and other body fluids. As such, physicians are less likely to prescribe injections in view of the

attendant risks to the healthcare personnel. Again, it may be due to a changing morbidity profile in Nigeria with the increase in non-communicable disease such as hypertension[27] and the change in antimalarial medicine policy that led to the removal of chloroquine from the recommended antimalarial medications [28] when compared with the time the reference values were developed[11]. There may be a need to revise the reference values in view of this change. We however note a higher than prevailing averages for UBTH and on further evaluation this was adduced to injections of antimalarial- artemether and use of paracetamol. There appears to be an urgent need to conduct another interventional study in antimalarial prescribing in that centre despite an initial study[29], especially since there has been a paradigm shift in the prescriptions of antimalarials to Artemisinin combination therapy (ACTs) in out-patient care than injectables[28]. It is assumed that for patients requiring injections, they would be referred to the appropriate points of care. The use of intramuscular antimalarials in out-patient care was also seen in a study in the Northern part of the country[30].

All institutions performed below 80% in prescribing medicines in the National Essential Medicines List. The EML is backed by law and is meant to encourage rational prescribing and reduce cost (direct and indirect)[31]. An earlier study had shown a high adherence to the EML up to 95%[12]. Non-adherence to this important policy may be an indication of the physician's preference for newer drugs as a consequence of drug promotion or it could be from personal research suggesting the superiority of newer molecules over the medicines in the national EML. Again, it may be due to lack of awareness of the Standard Treatment Guidelines (STG) as well as the EML. It has been demonstrated that most prescribers are unaware of the availability and usefulness of the EML, and for others, the list is unavailable for their use[6]. The results from this study has great implication for a developing nation with numerous drug challenges as it may lead to poor drug stocking practices, limiting access to real essential medicines. Worthy of note is the fact that a newer edition of the national EML was released recently after the completion of this study. A systematic review had shown that a less than optimal adherence is not an uncommon occurrence in sub-Saharan Africa[32].

We note the high use of paracetamol and diclofenac in this study as the singular most prescribed medications. Paracetamol is deemed to be safe and this may explain the high rate of prescriptions, but it has been recently shown that long term usage of paracetamol may have adverse consequences[33] and although the safety concerns regarding use of Non Steroidal Anti-inflammatory Drugs(NSAIDs) are relatively well known, the high rate of prescriptions in this study suggests there may be a need to educate the prescribers further about other lesser known risks and evaluate other commonly used medicines for their safety profile in this homogenous population. Overall this study has shown that medicines used in the treatment of non-communicable diseases may require close observations in view of the number of prescriptions seen in this study, without de-emphasizing the surveillance on antimicrobials especially antibiotics.

Limitations

This study was not intended to address the characteristics of prescribers which should have shed more light into prescriber factors that impact on the quality of the usage of medicines. Again the study does not capture some medicines (e.g. some antimicrobials) which are used largely or exclusively in the public health programs and are not seen in the out-patient departments.

Conclusion and relevance

This drug utilization study in teaching hospitals in the South-South zone of Nigeria still showed a less than optimal adherence to rational prescribing as evaluated with the use of the WHO-INRUD Prescribing Indicators as tool for the assessment. Observed values were not markedly different from found in earlier studies two to three decades ago. However, lower rates of injections and antibiotic prescribing was observed despite outliers in a few centres. There is need for an intensive, sustained intervention measures with reinforcement to effect a change in knowledge, attitude and practice.

Acknowledgements

We thank the management and staff of the various teaching hospitals especially the pharmacy departments for their kind assistance in carrying out this study.

Funding: Self funded

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CHAPTER 4:

KNOWLEDGE, ATTITUDE AND PRACTICE OF HEALTH PROFESSIONALS REGARDING PHARMACOVIGILANCE IN SOUTH-SOUTH NIGERIA.

Chapter 4 Knowledge, Attitude and Practice of health professionals regarding Pharmacovigilance in South-South Nigeria.

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Submitted to Pharmacoepidemiology and Drug Safety - April 2018

Key points

1. The health care professionals in Nigeria have a modest knowledge of the concept pharmacovigilance but not entirely about the product concerns relating to herbal medicines and over the counter preparations.
2. There was also a tendency to report life-threatening ADRs and reactions to newly marketed medicines but only a few would report mild ADRs.
3. Less than half of the respondents were aware of a local pharmacovigilance centre at their institutions.
4. Only 12.1% of the respondents had ever reported an adverse reaction with the adverse reaction reporting form while others used modalities such as the case records, ward report book and the pharmaceutical care sheet.
5. Previous training on ADR reporting as well as the medical profession were associated with ever - reporting an adverse reaction using the national adverse drug reaction reporting form.

Abstract

Purpose: In Nigeria, reporting pharmacovigilance issues especially adverse drug reactions (ADR) from health facilities is encouraged. This study evaluated the knowledge, attitude and practice of healthcare professionals (HCP) regarding pharmacovigilance in teaching hospitals in the South-South zone of Nigeria.

Methods: A cross-sectional study was conducted in six randomly selected teaching hospitals in the South-South zone of Nigeria. A semi-structured questionnaire was administered to HCPs involved in patient care (doctors, pharmacists and nurses). Information sought included demographics, knowledge, perception and practice of pharmacovigilance especially ADR reporting. Data was analyzed using descriptive and inferential statistics.

Results: Eight hundred and eleven healthcare professionals participated in the study with a response rate of 70.8%. The mean age (SD) was 39.0 (8.1) years and mean duration of practice (SD) was 12.7 (8.2) years. Thirty percent of HCPs had ever reported an ADR, of which only 12.1% had ever used the national ADR reporting form. Most respondents would submit ADR reports relating to new medicines (93.2%), vaccines (80.6%), new and unexpected ADRs (85.3%). However, fewer respondents would submit reports relating to herbal medicines (67.3%), medications errors (60.4%), and mild ADRs (32.1%). Most respondents (91.6%) believed they should report all ADRs. However, 40% had difficulties in determining whether to report. Increased awareness (27.6 %), education on ADR reporting (6.7%), reporting via the short messaging system (62.9%) were offered as solutions to improve reports.

Conclusion: The Nigerian healthcare professionals had a modest knowledge but poor reporting practices in pharmacovigilance which may improve with education and easier reporting avenues.

Introduction

Pharmacovigilance has been defined as '*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems*'[1]. The scope of pharmacovigilance has been widened to include other relevant issues such as medication errors, lack of effectiveness, abuse and irrational use of medicine[1] whilst the product concerns include herbals, complementary medicines and vaccines, biologicals etc.

Early detection and recognition of adverse drug reactions is a key element to the growth of pharmacovigilance especially in the area of spontaneous reporting of adverse drug reactions [2]. This method of pharmacovigilance remains the most accessible to healthcare professionals. Worldwide the number of reports in the database has grown remarkably with over 16 million Individual Case Safety Reports (ICSRs) in the WHO database as at February 2018. However, the number from low and lower middle income countries is still a bit suboptimal[3].

Underreporting has been shown to be a huge contributor to the dearth of report from the developing countries[4]. In a systematic review of 37 studies, it was demonstrated that the median rate of underreporting was 94% [5]. Ignorance of types of Adverse Drug Reaction (ADRs) that should be reported, diffidence, lethargy about reporting as well as lack of adequate information about recently marketed medicines are some of the factors that have been shown to contribute to this phenomenon. Others include difficulty in obtaining an ADR reporting form as well as the bureaucratic process in reporting[6,7].

The rate of reporting of ADRs has been found to be quite low in Nigeria considering that the National Pharmacovigilance Centre (NPC) of Nigeria has just over 18,000 reports in its database of ADRs since its inception in 2004 despite the implementation of an active pharmacovigilance system [8]. Lack of awareness and availability of the national ADR reporting forms (Yellow forms), cumbersome reporting processes, lack of knowledge of the location of reporting centers and who can report were some of the factors responsible for underreporting[9-14]. Others include the fear of litigation, lack of adequate time, and ignorance if reaction was actually an ADR[9–14]. Most of these studies have been carried out on physicians and very few on nurses or pharmacists although all health care professionals can report ADRs in Nigeria[15]. There have also been very few studies carried out in the South-South zone of the country.

Medicine related problems abound in Nigeria with a high use of herbal medicines, unrestricted use of prescription only medicines, fatal occurrences associated with substandard and falsified medical products use and a high burden (though not properly quantified) of ADRs[8]. The creation of the Zonal Pharmacovigilance Centers in 2012 (including the South-South Zonal Centre) to enhance reports and improve communication with the NPC makes it imperative to determine the perception of pharmacovigilance in the South-South zone with a view to using the information obtained for future intervention studies in the local as well as other resource limited settings.

Methods

Study setting and design: This study was carried out in the South -South Zone of Nigeria which is located in the coastal region of Nigeria. It comprises six states namely Akwa-Ibom, Bayelsa, Cross Rivers, Delta, Edo and Rivers with a population of 21,014,655 million persons (Nigeria national census 2006). The South-South Zonal Pharmacovigilance Centre is domiciled in the University of Benin Teaching Hospital, a tertiary hospital for service, learning and research.

In Nigeria, health care is delivered at three levels; primary, secondary and tertiary. Tertiary care hospitals which include teaching hospitals provide the highest level of care and serve as referral centres for the secondary and primary centres. This study was directed at the teaching hospitals because they provide the widest access to all patients with an inclusiveness of all cadres of healthcare professionals (HCP). In the South-South zone there are eight teaching hospitals, seven are government owned, and one privately owned.

Eligibility criteria: teaching hospitals were used to ensure inclusiveness of all clinical disciplines and staff complement. All six states in the zone were represented by a teaching hospital. An institutional approval was required from the Chief Medical Director / Management prior to inclusion in the study.

The study was subsequently carried out in 6 teaching hospitals randomly selected using a table of random numbers for all the states in the zone namely:

- University of Benin Teaching Hospital Benin-City, Edo State, (UBTH).
- Delta State University Teaching Hospital Oghara, Delta State, (DELSUTH).
- Niger Delta University Teaching Hospital Okolobri, Bayelsa State, (NDUTH).
- University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, (UPTH).
- University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State, (UUTH).
- University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH).

Study population: Healthcare professionals in each institution involved in patient care and in a position to report ADRs namely the doctors, pharmacists and nurses were invited to participate to the study. Only post registration HCPs were included in the study as the study measured the practice in the previous year. Students, interns were excluded from the study as they typically would be undergoing supervised training at the time of the study. Ethical and institutional approval was obtained from the various institutions as well as informed consent from each health professional. Consenting HCPs were included in the study and those who could not complete the questionnaire were treated as non-responders and were not included in the final analysis. The approximate number of post registration HCPs working in the selected hospitals who were eligible for inclusion into the study as at 2016 January were 4912 with doctors 2085 (42.4%), nurses 2662 (54.2%) and pharmacists 165 (3.4%).

Sample size calculation: In the study undertaken by Ogundele et.al[13], it was shown that 48% of the HCP in that study had reported an ADR at least once since qualification. The sample size for the study was calculated using the formula for estimating single proportions[16].

$$n = {}^{z^2 p(1-p)}/_{r^2}$$

Where the z value was taken as 1.96; p, proportion of positive attitudes, was assumed to be 48%; and r, the margin of error of estimation, was assumed to be 5% or 0.05. This provided a sample size of 400. To account for non-response as observed in the study by Ogundele et al[13] 15% was added, providing a calculated sample size of 460.

Data collection methods: All health care professionals including physicians, nurses and pharmacists, working in the institutions and directly involved in clinical services that consented to the study were contacted through their respective institutional heads and heads of department. Those who consented to the study were administered a semi-structured questionnaire which was developed after bibliographic and literature search from previous studies in this area [7,10,21,11–14,17–20] to evaluate their knowledge, attitude and practice of pharmacovigilance specifically ADRs reporting.

The questionnaire contained demographics of the HCPs such as age, duration of practice, gender, institution etc.
Furthermore, knowledge of ADR definitions, reporting schemes, questions regarding the location of the pharmacovigilance centre and the factors that may affect reporting were sought. Their perception of pharmacovigilance such as believing their reports made a difference in patients' safety, receiving incentives for reporting amongst others were also sought. Their practice of ADR reporting including if they have ever used the national ADR reporting form, the approximate number of reports sent in the previous month and year, as well as previous pharmacovigilance training was equally sought.
In defining an ADR, the keywords (noxious and unintended) had to be present to be regarded as a correct answer. Partially correct answers may contain one or the other and an incorrect answer did not contain any of the keyword or related synonyms. The various answers from open ended question were synthesized thematically and similar answers merged. Multiple responses were accepted. There were 12 questions for the assessment of the health professionals' knowledge, 10 questions relating to the attitude and 18 questions regarding their practice of ADR reporting.- Appendix I

The questionnaire was pre-tested in 25 health professionals from different hospitals who were attending a workshop on pharmacovigilance and had the questionnaire administered prior to the commencement of the workshop. They were asked about the relevance, wording and structure of the questionnaire and modifications were made to the final questionnaire.

Data Analysis

The study was analysed descriptively, with frequencies and means ± standard deviation used to describe continuous variables. The data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). The possible determinants of ever reporting an ADR using the Nigerian national ADR reporting form was done using chi square. The level of significance was set at a p value of 0.05.

Results

A total of 1200 questionnaires were distributed to Health Care Professionals (HCP) in the various teaching hospitals and 850 were retrieved, however 39 questionnaires were excluded from the analysis as the respondents were student nurses, medical interns who were not supposed to fill the questionnaire. A total of 811 respondents were eventually

studied with a corrected response rate of 70.8%. The mean age (SD) of the participating healthcare professionals was 39.0 (8.1) years and their mean duration of practice (SD) was 12.7 (8.2) years. The distribution of the type of health care professional of the respondents is as shown in Table 1. Fifteen persons did not indicate their HCP status (i.e. 1.8% of the respondents).

Table 1: Demographics of the Health Care Professionals

Characteristics	**All HCP N = 811**
Mean age (SD), years	38.97 (8.1)
Mean duration of practice (SD), years	12.66 (8.2)
Sex	
Males	297 (36.6)
Females	473 (58.3)
Unknown	41 (5.1)
Profession	
Doctors	373 (46)
Nurses	343 (42.3)
Pharmacists	80 (9.9)
Unknown	15 (1.8)

Knowledge of the scope of pharmacovigilance, adverse drug reaction reporting scheme and the definition of an adverse drug reaction.

One hundred and seventy respondents (21.0%) provided correct definition of an ADR while 106 (13.1%) and 430 (53.0%) respondents gave incorrect or partially correct definitions respectively. One hundred and five (12.9%) did not respond to the question. Among the pharmacists, 46.3% gave a correct definition of an ADR compared to 24.4% and 12% of doctors and nurses respectively (χ^2= 78.253, p<0.001) and pharmacists were most likely to give a correct definition p=<0.0001. Most HCPs felt that doctors (92.2%), pharmacists (90.4%) and nurses (89.4%) should be able to report ADRs. Furthermore, other categories of persons including patients (16.5%), any other allied health care worker (5.8%), anyone (5.5%), or others (2.9%) (i.e. laboratory technicians, community health extension workers, traditional medicine dealers, patent medicine dealers can also report ADRs. (Multiple responses were accepted).

Regarding the types of ADRs that could occur (Table 2), most of the respondents (85.3%) knew that an ADR could result from the pharmacological action of the drug (81.8%). More than half (59.2%) knew that ADRs can persist for a long time but only (35.5%) knew that ADR occurrence could be delayed. Furthermore, majority of respondents knew that ADRs could occur with newly marketed medicines (93.2%). Between 55 and 60% of respondent knew that cases of medication errors, drug abuse or dependence should be reported. About two-third (63.5%) of HCPs felt a life-threatening ADR should be reported. However, only one-third (32.1%) felt there was a need to report mild ADRs.

Table 2: Knowledge of the classification of ADRs and when to submit an ADR report by healthcare professionals in South- South zone of Nigeria.

Knowledge items about ADRs	n respondents = 811			
	Yes, n (%)	No, n (%)	Don't know, n (%)	No answer, n (%)
ADRs resulting from normal pharmacological action of drug	663 (81.8)	54 (6.7)	7 (0.9)	87 (10.7)
New and unexpected ADRs	692 (85.3)	30 (3.7)	4 (0.6)	85 (10.5)
ADRs persisting for a long time	480 (59.2)	98 (12.1)	31 (3.8)	202 (24.9)
ADRS delayed for a long time	288 (35.5)	209 (25.8)	88 (10.9)	226 (27.9)
ADRs occurring as follows:				
- at the end of use of medicines	464 (57.2)	160 (19.7)	36 (4.4)	151 (18.6)
- a newly marketed medicine	756 (93.2)	10 (1.2)	5 (0.6)	40 (4.9)
- an established medicine	674 (83.1)	29 (3.6)	12 (1.5)	96 (11.8)
- herbal medicine	546 (67.3)	54 (6.7)	49 (6.0)	162 (20.0)
- biological medicine	561 (69.2)	26 (3.2)	52 (6.4)	172 (21.2)
- complementary medicine	546 (67.3)	29 (3.6)	67 (8.3)	169 (20.8)
- vaccine	654 (80.6)	18 (2.2)	9 (1.1)	130 (16.0)
- over the counter preparations (OTCs)	634 (78.2)	33 (4.1)	16 (2.0)	128 (15.8)
- when used by children	606 (74.7)	30 (3.7)	15 (1.8)	160 (19.7)
Medicines misused or used with error	490 (60.4)	140 (17.3)	28 (3.5)	153 (18.9)
In cases of drug abuse	449 (55.4)	150 (18.5)	46 (5.7)	164 (20.2)
In cases of drug dependence	459 (56.6)	127 (15.7)	48 (5.9)	177 (21.8)
Report mild ADRs	260 (32.1)	321 (39.6)	28 (3.5)	202 (24.9)
Report life threatening ADRs	515 (63.5)	236 (29.1)	4 (0.5)	56 (6.9)

ADR: Adverse Drug Reaction, OTC: Over The Counter.

Awareness of Pharmacovigilance Centers

Three hundred and ninety-nine (49.2%) respondents were aware of the existence of a local pharmacovigilance centre in their institution but only (22.1%) had ever visited the centre. Of these, more pharmacists visited the centre (45.5%) compared with the doctors (31.8%) and the nurses (22.7%) (X^2= 83.75, p< 0.001)

More specifically, only 26.6% HCPs were aware of existence of the South-South Zonal Pharmacovigilance Centre. Awareness of the existence of the National Pharmacovigilance Centre was reported by 51.5% of the respondents, of which 32.9% knew the exact location of the headquarters. Pharmacists had a significant highest level of awareness of the National Pharmacovigilance Centre (85.0%) compared with doctors (59.2%) and nurses (34.4%) (X^2= 99.49, p < 0.001). Two hundred and eighty-three (34.9%) respondents were aware of the ADR reporting form. Of these, 76.3% admitted to have seen the form.

Attitudes toward reporting of ADRs

In reviewing the positive attitudes relating to ADR reporting, most respondents (91.6%) believed they should report all ADRs, that it was their professional obligation to report (91.1%) and about half (56.4%) of the HCP believed they had no difficulty in determining if an ADR had occurred in a patient. (Table 3).

Table 3: Attitudes of Healthcare professionals in the South- South zone towards reporting adverse drug reactions.

Attitude items towards ADR reporting	respondents n = 811
	n (%)
Belief that all ADRs should be reported	743 (91.6)
Professional obligation to report	740 (91.2)
ADR reporting does not put career at risk	739 (91.1)
Reporting should be made mandatory	728 (89.8)
ADR reporting should not be for publishing only	721 (88.9)
Not expecting to receive incentives for reporting	614 (75.7)
Reporting when unsure if ADR has occurred	591 (72.9)
Reporting when not sure it will make a difference	559 (68.9)
No difficulty in determining occurrence of ADR	456 (56.2)

ADR: Adverse drug Reaction.

Three hundred and twenty two (39.7%) respondents, found it difficult to determine if an ADR had occurred. Of these, only 25% gave the following reasons for their difficulty: use of multiple medicines by the patients and possibilities of drug-drug interactions (28.4%), (Table 4) (Multiple responses were accepted).

Table 4: Factors reported as difficulties in determining ADR occurrence by HCP in the South-South zone.

Factors related to difficulty in reporting, n = 81	n (%)
Polypharmacy and possible drug-drug interactions	23 (28.4%)
ADR may mimic the constitutional symptoms of the disease	21 (25.9%)
Patients do not report ADR	22 (27.2%)
Herbal medicine use by patients	3 (3.7%)
Inability to identify the drug	2 (2.5%)
Lack of training in ADR recognition	4 (4.9%)
Loss of monitoring and follow up of patients after they have had drugs prescribed	4 (4.9%)
Unknown reactions	8 (9.9%)

Others include: 5(6.2%) (Uncertainty about drug history, Difficult to establish causality, Uncommon reactions. Presence of Co-morbid states, Medication error-(overdose especially). Poor facilities to identify ADR cases.) ***ADR:*** *Adverse Drug Reaction*

Ninety percent of the respondents felt ADR reporting should be made mandatory for all health care professionals, for the doctors (90.1%), the pharmacists (87.1%), the nurses (80.1%), and the dentists (76.5%). Very few respondents 27 (3.3%) felt reporting ADR puts their careers at risk and gave the following reasons for their choice: risk of punitive measures against the reporter (n = 6), perception of the health care worker as incompetent/negligent (n=4), others (n=5) include fear of litigation, fear of inter-professional rivalry between pharmacists and doctors, liability of the pharmaceutical company, violent reactions from relations if death occurs.

Practice of Pharmacovigilance

Six hundred and sixty-three HCPs (81.8%) stated that they had already observed an ADR. However, only 30.1% had ever reported one. Of those reporting, the different modes of report included the use of the national ADR reporting form in (40.2%), the patients' case record (21.7%) and the ward report book (35.7%). A verbal report to the doctor, pharmacist or senior colleague was reported by 14.3% and a case report by 3 respondents, others were patient's treatment sheet, critical event form and pharmaceutical care daily worksheet. Nurses were less likely to report with the yellow form (10.3%) as compared to doctors (57.7%) and pharmacists (97.7%) (X^2=116.56, p<0.001) (Table 5).

Table 5: Modes of reporting adverse drug reactions by the various categories of healthcare professionals among those who have reported an ADRs

	Doctors, n=71	Nurses, n =126	Pharmacists, n=44	Unknown n=3	Total, n=244	Chi square	p-value
Mode of report, n (%)							
Yellow form	41 (57.7)	13 (10.3)	43 (97.7)	1 (33.3)	98 (40.2)	116.56	<0.001
Case note	25 (35.2)	27 (20.6)	2 (4.5)	0(0.0)	53 (21.7)	16.153	0.001
Ward report book	2 (2.8)	84 (66.7)	1 (2.3)	0(0.0)	88 (35.7)	109.224	<0.001

Among the 98 respondents who had reported an ADRs using the national ADR reporting forms, 8.2% sent the forms to the National Pharmacovigilance Centre (NPC), to a local Pharmacovigilance centre (69.4%), to a pharmacy department (12.2%), dropped the forms in ADR reporting boxes in wards or clinic or gave them to the unit head (4.1%), or forwarded them to the Institute of Human Virology Nigeria (3.1%). The health professionals recalled reporting an estimated total number of 235 ADRs the previous year and 38 ADRs in the previous month using the national ADR reporting form.

Among the 98 respondents who had ever reported an ADR using the national ADR reporting form, 60.2% found it easy accessing the ADR forms and gave the following reasons: forms easily accessible in clinics and the wards (37.3%), or available from the Drug Information Centre (11.9%), or available in pharmacy units (10.2%), and also accessible from the public health programs (4.2%), while 30.5% gave no reason. Thirty-four respondents (34.7%) however found ADR form accessibility-difficult and for the following reasons; poor accessibility at the point of use (44.1%), poor awareness of the location of the pharmacovigilance centre or committee to obtain the form (14.7%), lack of time and shortage of forms (14.7%) and no response (32.4%). Reporting with the form was found to be easy by 81.6% of respondents and gave the following reasons: form was

straightforward and easy to understand (50%), needed information available (15%), previous training (7.5%). However, nine (9.2%) of respondents found the process difficult and they ascribed this to the form being too time consuming or having too many questions. Some others preferred to report verbally or use an e-version. Other reasons proffered related to the form not being self-explanatory, the difficulty in computing date reaction stopped. Most respondents gave no reasons for their answers.

To assess the process of returning the form, 55.1% of respondents found it very easy or easy returning the form. Others were neutral (28.6%), found it difficult or extremely difficult (7.1%).

Training and Factors to improve ADR reporting

Among the study respondents, 78.4% had not received any training in ADR reporting. Of those who had received some training Pharmacists were more likely to have been trained in pharmacovigilance and ADRs reporting (X^2 =120.43, $p<0.001$). Respondents who benefited from a previous training in pharmacovigilance were more likely to ever report an ADR (X^2 =67.69, $p<0.001$).

The following reasons were offered as ways to improve ADR reports in their centres, increased awareness (27.6%), education on ADR reporting (6.7%), improve accessibility to the reporting forms (4.7%), filling of ADR forms on the internet (1.8%), streamlining the process of returning ADR forms (2.0%). Other possible avenues for improving reporting of ADRs explored in this study revealed that filling via short messaging system (SMS) was preferred by 62.9%, via the internet by 48%, by direct link to the South -South Zonal Pharmacovigilance Centre via phone by 75.2% and for 62.5% via email.

Analyzing the health care professionals who had reported an ADR using the national ADR form, the following variables were found to have a significant association with reporting - the male sex, cadre of health care professional- pharmacists, not willing to receive incentives for reporting by the HCP as well as previous training on ADR reporting. Other variables were not significant (Table 6).

Table 6: Factors associated with reporting of adverse drug reactions using the national adverse drug reaction form.

Characteristic	Reported using the ADR form, n (%)	Never reported using the ADR form, n (%)	χ^2	p value
Gender				
-Males	51 (17.2)	246 (82.8)	12.182	0.002
-Females	45 (9.5)	428 (90.5)		
-Unknown	2 (4.9)	39 (95.1)		
Cadre of HCP				
-Doctors	41 (11.0)	332 (89.0)	153.774	<0.001
-Pharmacists	43 (53.8)	37 (46.3)		
-Nurses	13 (3.8)	330 (96.2)		
Unknown	1 (6.7)	14 (93.3)		
Previous PV training				
- Yes	43 (33.9)	84 (66.1)	67.690	<0.001
-No	50 (7.9)	586 (92.1)		
-Don't know	0(0.0)	2(100.0)		
-No response	5 (10.9)	41 (89.1)		
Willingness to receive incentives				
-Yes	11 (9.2)	109 (90.8)	11.467	0.009
-No	72 (11.7)	542 (88.3)		
-Don't know	14 (25.5)	41 (74.5)		
-No response	1 (4.5)	21 (95.5)		

HCP: Health Care Professional, ADR: Adverse Drug Reaction. PV: Pharmacovigilance

Discussion

This study was aimed at evaluating the KAP of health professionals in the South -South zone regarding pharmacovigilance. The study had a high number of participants and more importantly a high number of participating nurses, who had hitherto not been very active in reporting ADRs in Nigeria [13]. The study shows that the reporting of ADRs is still quite low regardless of the mode of reporting and even fewer reporters have used the national ADR reporting form. This has been seen in preliminary studies limited to single health care facilities in Nigeria[11,13,14,22,23], and none has been carried out at the zonal level in the country. Our study is the first in-depth analysis of the perception of health care professionals in the South-South zone of Nigeria. A similar trend of poor reporting of ADRs was also observed worldwide[24–27].

The knowledge base of the HCP regarding certain aspects of pharmacovigilance was explored in this study. The respondents displayed poor knowledge regarding certain concepts in pharmacovigilance such as delayed ADRs, end of use ADRs, ADRs resulting from herbal medicine use, medications errors, drug dependence and drug misuse and abuse. This may be due to the perception that such cases did not qualify as safety concerns. Poor recognition may lead to underestimation of data and poor quantification of the attendant risks. There is a need to sensitize the professionals towards identification of delayed ADRs as notable ADRs that were delayed were identified due to a high index of suspicion by the physicians[28].

A good proportion of respondent had an awareness about the local pharmacovigilance and National Pharmacovigilance Centre, (NPC) but not the exact location, this is similar to what was reported in another Nigerian study [29] and implies that the awareness campaigns by the NPC has yielded some positive benefits. However, lack of knowledge of the exact location may hinder reporting timelines as reports may be directed to the wrong locations. There was generally a poor awareness of the South- South Zonal Centre; this may not be unrelated to the fact that the zonal centres were newly created and as such yet to become fully operational. Regionalisation of centres is meant to improve reports[30] therefore it is hoped that more awareness campaigns be carried out in the zone.

The study also highlighted those who could report ADRs and respondents also felt patients, traditional medicine practitioners, as well as patent medicine dealers should report ADRs as a high number of patients do patronize these outlets and this will improve patient safety. However, there will be a need to carry out an assessment of the reports that may emanate from these quarters in order to have useful data. Reporting by patients is already being encouraged in Nigeria[8].

Evaluating attitudinal factors in this study also reflected why there might have been poor reporting of ADRs as it has been shown that attitudinal reasons are about the strongest determinants of underreporting[7,31]. The fear of litigation and punitive measures were also important reasons that contributed to poor reporting in this study. This may be related to a general morbid fear of disclosures of medication related issues and poor understanding of the mechanisms of ADRs. The health professionals may have to be properly educated about the ethics and legal aspects involved in health care. It is noteworthy that most of the respondents do not expect incentives for reporting. This is an important factor that needs to be highlighted in order to encourage the HCPs that are interested in patient safety

despite studies that have shown that incentives may improve reporting[32,33], a resource challenged setting like ours may be unable to meet such a goal.

The poor reporting practice observed in this study has also been shown elsewhere [13,34], it was observed that pharmacists appeared to have better reporting practices than the other cadres of healthcare professionals, this may be due to the proximity of the drug information centres to their practice area as well as the possibility of previous training[13,23]. The use of the ward report book in ADR evaluation in our setting may be an avenue to increasing the number of ADRs in the database as more nurses utilized this medium as seen in other studies [11,13].

The limitations experienced by some of the respondents in processing the adverse reaction form may account for the few reports sent by the respondents. This highlights a need to have regular monitoring and evaluation of the pharmacovigilance system in order to improve the reporting process and the quality of the reports. The routine use of pharmacovigilance indicators will enable the institution and the NPC improve the system[35,36].

Previous training and the profession of the HCP were associated with reporting using the national ADR reporting form and this was reflected in the various ways to improve ADR reporting proffered by the HCP such as repeated training, education of the HCP, and feedback as shown in other studies[33,37,38] .

A few limitations were encountered in this study; we noted a high proportion of non-response in the assessment of knowledge of pharmacovigilance in this study, but this may have been due to the relative lack of knowledge of the particular items in the questionnaire as there was differential lack of response to the different questions. It also highlighted the areas that may need further analysis in future studies. The study was also conducted in teaching hospitals only since these are the hospitals where pharmacovigilance has just been introduced in the country but we feel the results could be generalized and may be similar to what obtains in other hospitals in the zone.

Conclusion

In all, the health professionals working in the South-South zone have a fair knowledge of pharmacovigilance and mostly on ADRs although with poor reporting practices. Education, awareness and a general change in perception may be required to improve the reports from this zone.

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CHAPTER 5:

EDUCATIONAL INTERVENTION TO IMPROVE THE KNOWLEDGE, ATTITUDE AND PRACTICE OF HEALTH CARE PROFESSIONALS REGARDING PHARMACOVIGILANCE IN SOUTH-SOUTH NIGERIA.

Chapter 5 Educational intervention to improve the knowledge, attitude and practice of Health Care Professionals regarding pharmacovigilance in South-South Nigeria

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Accepted for publication in Therapeutic advances for Drug Safety in November 2018

Abstract

Introduction: This study set out to evaluate the effect of a combined educational intervention and year-long monthly text message reinforcements via the Short Messaging System (SMS) on the knowledge, attitude and practice of Healthcare Professionals (HCPs) towards pharmacovigilance.

Methods: Six randomly selected teaching hospitals in the South-South zone of Nigeria were randomized in 1:1 ratio into intervention and control groups. The educational intervention consisted of delivering a seminar followed by sending monthly texts message reinforcements via SMS over 12 months. Then a semi-structured questionnaire regarding the Knowledge, Attitude and Practice (KAP) of pharmacovigilance was completed by HCPs working in the hospitals after the intervention. Data was analyzed descriptively and inferentially.

Results: A total of 931 HCPs participated in the post intervention study (596 in the intervention and 335 in the control). The M: F ratio was 1:1.5. According to the KAP questionnaire, a significant difference was observed between the intervention and control groups, regarding knowledge of the types of Adverse Drug Reactions (ADRs). ADR resulting from pharmacological action of the drug (85.6% vs. 77%, p=0.001), the fact that ADRs can persist for a long time; (60.1% vs. 53.4%, p=0.024) and a higher awareness of the ADR reporting form (48.7% vs. 18.8%, p<0.001). Most respondents in the intervention group (68.5% vs. 60.6%, p=0.001) believed they should report ADRs even if they were unsure an ADR has occurred, a greater proportion of HCPs from the intervention group had significantly observed an ADR (82% vs. 73.4%, p=0.001). Furthermore, of the 188 who had ever reported an ADR, 41% from the intervention group used the national ADR reporting form as compared with 19.8% from the control (p<0.001).

Conclusion: This educational intervention and the use of SMS as a reinforcement tool appeared to have positively impacted on the knowledge and practice of pharmacovigilance in South-South Nigeria with a less than impressive change in attitude. Continuous medical education may be required to effect long lasting changes.

Key words: Pharmacovigilance, Adverse Drug Reaction reporting, Educational Intervention, Healthcare Professionals, knowledge, attitude and Practice, SMS. Nigeria

Introduction

The scope of pharmacovigilance has increased over the years from reporting mainly adverse drug reaction (ADR) to reporting cases of medication errors, misuse of medicines, drug dependence, and lack of effectiveness among others [1]. The product concerns have also been expanded to include herbal medicines, biologics, vaccines as well as blood products [1]. The main form of reporting remains the spontaneous method of reporting which has been beset with the issue of under-recognition and under-reporting of the ADRs especially with the increased scope and newer product concerns [2] and especially in Africa where the recognition of drug related events appears to be poor as medicines are associated only with the benefits they render and not the harmful effects that may ensue from them[3].

Pharmacovigilance is an important and gradually developing discipline in Nigeria that has been strengthened by the development of key policy documents such as the National drug policy and recently the National pharmacovigilance policy [4 5]. To encourage this growth, the National Pharmacovigilance Centre (NPC) has been active by engaging the media to disseminate awareness to the general public, organizing pharmacovigilance training to various cadres of health care professionals over the years and in different tiers of institutions since joining the international drug monitoring program in 2004 [6,7]. The growth of the pharmacovigilance system rests basically on the capacity development of the health care professionals as well as education of the public [1].

In Nigeria, preliminary single institutional studies have also shown ignorance of procedures in reporting, lack of knowledge of the Nigerian national reporting forms as well as difficulty in determining the occurrence of an adverse drug reaction or lack of willingness in reporting a well-known reaction were some of the factors that may be responsible for under-reporting [8–10]. Furthermore, according to National Pharmacovigilance Centre's (NPC's) guide to reporting adverse drug reactions,[11] all health care professionals can forward ADR reports. Education of the health care professionals on recognition and reporting of the drug related events is essential towards ensuring increased numbers as well as improving the quality of ADR reports [12].

Educational strategies towards improving the knowledge and attitude of the health care professionals have been carried out in different parts of the world using different methods. These include the use of didactic lectures, presentations, posters relating to pharmacovigilance and adverse drug reaction reporting, different modes of reminders, use of safety bulletins and safety newsletters amongst others [13–17]. Rates of success of the strategies varied depending on the type of health care professionals. It has also been shown that a multi-dimensional approach to changing provider behaviour is key to a successful intervention [18].

In resource constrained settings, interventional strategies which are easily delivered such as the use of the short messaging system (SMS) in sending reminders may be useful to improve knowledge of pharmacovigilance in healthcare professionals [16,19]. In Nigeria, mobile phone penetration is quite high and no study has evaluated the impact of training and SMS monthly reinforcements on improving the knowledge, attitude and practices pertaining to pharmacovigilance despite findings that suggest that increased awareness and training may improve the practice of pharmacovigilance [13]. This study therefore set out to evaluate the effect of a combined educational seminar and year-long monthly SMS reinforcements on the knowledge, attitude and practice of pharmacovigilance of healthcare professionals practicing in the South-South zone.

Methods

Setting

The study was conducted in teaching hospitals which are tertiary care centres in the South-South geopolitical zone of Nigeria, located in the coastal region of Nigeria and home to about 21 million residents (National census 2006). The zone is comprised of 6 states – Akwa- Ibom, Bayelsa, Cross-Rivers, Delta, Edo and Rivers State. All hospitals have a complement of doctors, pharmacists and nurses to cater to the health needs of the populace.

Design

A repeated cross-sectional study with teaching hospitals randomized to intervention and control sites was conducted from January 2016 to April 2017. This design was selected in view of the high probability of loss to follow up, exit of resident doctors from the program and posting of some other members of staff to out-stations [20]. The study now consisted of two sets of participants both before and 12 months after the intervention to account for the dynamics in a teaching hospital setting.

Selection of facilities and randomization

A sampling frame of all tertiary hospitals in the zone was obtained to include teaching hospitals, Federal medical centers as well as specialist hospitals that have a particular focus for treatment such as neuro-psychiatric hospitals. Teaching hospitals were selected for the study as they provided the widest access to both patient and health care professionals complement and were also in a position to train different cadres of undergraduates and post graduates. There were eight teaching hospitals in the zone and then 6 teaching hospitals were randomly selected using a table of random numbers with one teaching hospital representing a state. Other tertiary hospitals in the zone were excluded from the study as they were not teaching hospitals. To be included in the study, ethical and institutional approval was required from the ethics and research committee and Chief Medical Director of the institution respectively. Six institutions were included into the study namely: University of Benin Teaching Hospital Benin-City, Edo State, (UBTH); Delta State University Teaching Hospital Oghara, Delta State (DELSUTH); Niger Delta University Teaching Hospital Okolobri, Bayelsa State, (NDUTH); University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, (UPTH); University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State (UUTH) and University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH)). They were randomized in a 1:1 ratio into either intervention or control groups prior to commencement of the study following ethical and institutional approval.

Interventions

An intervention was implemented both at the level of the hospital and to individuals in the hospitals belonging to the intervention , namely : University of Benin Teaching Hospital Benin-City, Edo State, (UBTH); University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State (UUTH) and University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH)).

Educational intervention

The design and effectiveness of an educational intervention in changing behaviour of healthcare workers has been discussed in various studies [18,21,22]. The design here consisted of an active intervention with a seminar presentation followed by a passive year-long

regular intervention (monthly broadcast of text messages). The positive impact of a mixed effect of continuous medical education and other forms of intervention in changing health care workers behaviour has also been described [23]. All post-registration health care professionals working in the selected teaching hospitals were eligible to be recruited into the study if they consented to participate in either the baseline study or the repeat cross sectional study. The HCPs gave consent by filling the questionnaire and indicated their willingness for future contacts. We also allowed for those who attended the seminar to receive text messages if they so indicated. House-officers, pharmacy interns and students were excluded from the study as they were undergoing supervised training at the time. Only consenting HCPs were recruited into the study after stratification into the various professional cadres.

The seminar was an hour-long presentation delivered to the health care professionals at specially organised meetings. It was in two parts - firstly the scope and aims of pharmacovigilance were outlined using the WHO documents on pharmacoviglance[1,11,24], The definitions of the different key items of the ADRs [25,26], then the historical aspect of adverse drug reactions and relevant history of pharmacovigilance in Nigeria was described. The number of reports presently in the Nigerian database with the system organ classification and pharmacological classification was made known.

Secondly emphasis was laid on adverse drug reaction reporting, types of reports, reasons to report, how to report and other reporting modalities. The submission processes and consequences as well as frequently asked questions in adverse drug reaction reporting were presented. Finally, an algorithm of the adverse drug reaction reporting process was explained and the contacts of relevant persons and institutions listed. Posters and handbills regarding pharmacovigilance from the National Pharmacovigilance Centre were shared after the lecture. Short text messages reminding the HCPs to report all adverse drug reactions and the contacts details of the local pharmacovigilance centre personnel were sent to the health care professionals in the institutions monthly over 12 months after the educational intervention. This commenced immediately after the educational seminars. **Supplemental information 1.**

The educational seminar took place between January 2016 and March 2016 in the three intervention hospitals. The presentation was given by one of the researchers (AOO)

The participants in the control institutions received news from the national pharmacovigilance centre as usual and they could also report ADRs to their local pharmacovigilance centres.

Questionnaire

A semi-structured questionnaire which was developed after bibliographic and literature search from previous studies in this area [8,9,22,27–34] to evaluate their knowledge attitude and practice of pharmacovigilance specifically adverse drug reactions reporting was used.

The questionnaire had been pre-tested in 25 health professionals from different hospitals who were attending a workshop on pharmacovigilance. They were asked about the relevance, wording and layout of the questionnaire and modifications were made to the final questionnaire which contained 40 questions including some open-ended questions. It was also reviewed by other Clinical Pharmacologists in the area. The answers to the open-ended questions were synthesised and analyzed thematically.

The questionnaire contained demographics of the health care professionals such as age, duration of practice, gender, institution. Also, knowledge of adverse drug reaction definitions, reporting schemes, questions regarding the location of the pharmacovigilance centre was equally sought. Perception of pharmacovigilance such as determining the occurrence of an ADRs, willingness to receive incentives for reporting, belief that ADR reporting may place career at risk among others were also sought. Furthermore, they were also asked about previous ADR reporting, process of handling the ADR reporting form and other adverse drug reaction reporting practices in their hospitals.

There were 12 questions for the assessment of the health professionals' knowledge; 10 questions relating to the attitude and 18 questions regarding their practice of adverse drug reaction reporting. (Appendix I)

In both intervention and control sites, the questionnaire was initially (pre-intervention) administered to healthcare professionals to evaluate their baseline Knowledge Attitude and Practice of pharmacovigilance specifically adverse drug reactions reporting at the onset of the study, it was also administered at the end of the intervention, a year after the lecture and receipt of SMS (post-intervention).

Statistical analysis

Sample size

To calculate sample size for this randomized study and to get the required sample size per s with a power of 1 - □, (80%) and to detect a difference of d, the sample size (n) we estimated the sample size for individual randomized study comparing two proportions using Epi info version 7 software (CDC) [35]. The proportion of those who had used the national form to ever report an ADR using the national adverse drug reaction reporting form was about 26% in a previous study[9] and hoping that the intervention would improve the prevalence by 40% at a power of 80% and a 95% confidence interval. The estimated sample size for each of the study was 178 HealthCare Professionals and cumulatively 356. A 15% non-response rate was anticipated and this increased the sample size to 410 persons (205 per arm).

Data Analysis

The study was analyzed descriptively using frequencies and proportions. In defining an adverse drug reaction, the key elements (noxious and unintended) had to be present to be regarded as a correct answer. Partially correct answers may contain one or the other and an incorrect answer need not contain any of the key elements or related synonyms. The various answers from open ended question were synthesized thematically and similar answers merged (multiple responses were accepted). Chi-square was used to assess categorical variables and the significance value set at 0.05. SPSS version 21 was used for the analysis of the study.

Ethical consideration

Ethical approval was obtained from the research and ethics committee of all the selected institutions: Delta State University Teaching Hospital Oghara :DELSUTH/HREC/2015/024, Niger Delta University Teaching Hospital Okolobri, :NDUTH/REC/0005/2015, University of Benin Teaching Hospital Benin-City: UBTH:ADM/E22/2/VOL.VII/1245, University of Calabar Teaching Hospital, Calabar: UCTH/HREC/33/360, University of Port Harcourt Teaching Hospital, Port Harcourt :UPTH/ADM/90/S.II/VOL.X/668 and University of Uyo Teaching Hospital, Uyo: UUTH/AD/S/96/VOL.XIV/357. Written Informed consent was obtained from each

individual in the study. The participants were assured that their responses would be kept confidentially and not shared with third parties. All ethical considerations were observed. A further institutional approval was obtained from the management of the hospitals.

Results

The approximate number of post registration HCPs working in the selected hospitals who were eligible for inclusion into the study as at 2016 January were 4912 with doctors 2085 (42.4%), nurses 2662 (54.2%) and pharmacists 165 (3.4%). There were 3099 HCPs in the intervention arm and 1813 in the control arm. Only about a third of the HCPs in the intervention arm participated in the intervention despite an invitation sent to all HCPs.

In all, a total of 811 HCPs (65%- intervention and 35% -control arms) participated in the pre-intervention study in 2016 (response rate of 70.8%) and 931 HCPs in the repeated cross-sectional study with a response rate of 77.6 % (64% - intervention and 36%-control)..The HCPs who participated to the pre- and post-intervention surveys were very similar. However, mean age was slightly higher in the control group and there were more doctors participating. Table 1

Table 1: Characteristics of Health Care Professionals (HCPs) between the intervention and control groups, (n, %).

Characteristics	Pre-Intervention			Post-Intervention		
	Intervention (n=524)	Control (n=287)	p-value[1]	Intervention (n=596)	Control (n=335)	p-value[1]
Age, years- Mean (SD)	38.9 (7.9)	39.1 (8.4)	0.825	37.4 (7.9)	39.8 (7.9)	<0.001
Years of practice (SD)	12.5(8.3)	12.8 (8.1)	0.604	9.8 (6.8)	9.6 (6.9)	0.737
Gender						
Women	292 (55.7)	181 (63.1)		339 (56.9)	168 (50.1)	
Men	203 (38.7)	94 (32.8)	0.122	232 (38.9)	156 (46.6)	0.072
Unknown	29 (5.5)	12 (4.2)		25 (4.2)	11 (3.3)	
Type of HCP						
Doctors	238 (45.4)	135 (47.0)	0.938	281 (47.1)	165 (49.4)	0.005
Nurses	224 (42.7)	119 (41.5)		270 (45.3)	131 (39.2)	
Pharmacists	53 (10.1)	27 (9.4)		31 (5.2)	35 (10.5)	
Unknown	9 (1.7)	6 (2.1)		14 (2.3)	3 (0.9)	

[1]: p-value from Pearson Chi-square, HCP- Healthcare Professional.

Knowledge of Pharmacovigilance (scope and product concerns) (Table 2)

In evaluating the HCPs knowledge of pharmacovigilance, no significant difference was found between the groups as regards the pre-intervention questionnaire.

From the post-intervention questionnaire, there was a significant increased knowledge for several items between the groups. The following were better known by the HCPs from the intervention group: “ADR can result from the pharmacological action of the drug”; “ADRs can persist for a long time”; “ADR can occur with newly marketed medicines, vaccines, biological medicines, “Reports of cases of drug abuse or drug dependence”. Furthermore, regarding knowledge of what to report, most respondents in the intervention group would more likely submit reports of life threatening ADRs.

Knowledge of reporters and pharmacovigilance centers (Table 3)
There was a significant increased awareness of the existence of the South-South Zonal Pharmacovigilance Centre as well as the national ADR reporting form between the intervention and control groups according to the post-intervention questionnaire. In the pre-intervention survey, most of the respondents believed all cadres of healthcare professionals could report ADRs with doctors being the preferred group from the pre-intervention. However, from the post intervention questionnaire, it appeared that only those in the control still preferred doctors to report.

Attitude of health care workers (Table 4)
Attitude before the intervention was not significantly different between the groups. According to the post-intervention questionnaire, respondents in the control group had a significantly higher proportion of positive attitudes than in the intervention group, for most of the items regarding ADR reporting apart from reporting when not certain an ADR has occurred. However, belief about the importance of reporting ADRs was not different between the groups.

Table 2: Knowledge of types of ADR and product concerns of Pharmacovigilance of HealthCare Professionals between intervention and control groups, before and after the intervention, n (%)

Knowledge items	Pre-intervention Intervention (n =524) Yes n (%)	Pre-intervention Control (n = 287) Yes n (%)	p-value	Post Intervention Intervention (n=596) Yes n (%)	Post Intervention Control (n=335) Yes n (%)	p- value
Correct definition of ADR	111 (21.2)	59 (20.6)	0.894	47 (7.9)	19 (5.7)	0.123
Resulting from normal pharmacological action of drug	424 (80.9)	239 (83.3)	0.790	510 (85.6)	258 (77.0)	**<0.001**
New and unexpected ADRs	455 (86.8)	237 (82.6)	0.360	478 (80.2)	248 (78.0)	0.056
ADRs persisting for a long time	316 (60.3)	164 (57.1)	0.437	358 (60.1)	179 (53.4)	**0.024**
ADRs delayed for a long time	189 (36.1)	99 (34.5)	0.369	228 (38.3)	104 (31.0)	**0.028**
ADRs occurring in the following:						
at the end of use of medicines	303 (57.8)	161 (56.1)	0.798	372 (62.4)	202 (60.3)	0.257
a newly marketed medicine	486 (92.7)	270 (94.1)	0.843	542 (90.9)	267 (79.7)	**<0.001**
an established medicine and vaccine	436 (83.2)	238 (82.9)	0.090	480 (80.5)	244 (72.8)	**<0.001**
herbal medicine	343 (65.5)	203 (70.7)	0.319	406 (68.1)	241 (71.9)	0.183
biological medicine	358 (68.3)	203 (70.7)	0.267	386 (64.8)	240 (71.6)	**0.046**
complementary medicine	349 (66.6)	197 (68.6)	0.414	397 (66.6)	224 (66.9)	0.454
vaccine	426 (81.3)	228 (79.4)	0.889	447 (75.0)	247 (73.7)	**0.030**
over the counter preparations (OTCs)	411 (78.4)	223 (77.7)	0.995	433 (72.7)	287 (85.7)	**<0.001**
when used by children	393 (75.0)	213 (74.2)	0.823	431 (72.3)	253 (75.5)	0.604
medicines misused or used with error	319 (60.9)	171 (59.6)	0.538	399 (66.9)	225 (67.2)	**0.030**
In cases of drug abuse	279 (53.4)	170 (59.2)	0.370	388 (65.1)	205 (61.2)	**0.024**
In cases of drug dependence	286 (54.6)	170 (60.3)	0.471	376 (63.1)	196 (58.5)	**0.037**
Report mild ADRs	172 (32.8)	88 (30.7)	0.227	226 (37.9)	100 (29.9)	0.082
Report life threatening ADRs	346 (66.0)	169 (58.9)	0.242	436 (73.2)	218 (65.1)	**<0.001**

SSZPC- South-South Zonal Pharmacovigilance Centre, NPC, National Pharmacovigilance Centre, ADR- Adverse Drug Reaction

Table 3: Awareness of pharmacovigilance centers and reporting status of HealthCare Professionals between intervention and control groups, before and after the intervention, n (%)

	Pre-intervention			Post-Intervention		
	Intervention (n=524)	**Control (n=287)**	**p-value**	**Intervention (n=596)**	**Control (n=335)**	**p-value**
Awareness of the local pharmacovigilance centre	322 (61.5)	77 (26.8)	**<0.001**	345 (57.9)	135 (40.3)	**<0.001**
Awareness of the SSZPC	162 (30.9)	54 (18.9)	**<0.001**	273 (45.8)	78 (23.3)	**<0.001**
Awareness of the NPC	282 (53.8)	128 (45.1)	0.054	294 (49.3)	198 (59.1)	**0.009**
Awareness of the ADR reporting form	199 (38.0)	84 (26.6)	0.047	290 (48.7)	63 (18.8)	**<0.001**
Doctors to report	481 (91.8)	267 (93.0)	0.737	517 (86.7)	315 (94.0)	**0.006**
Nurses to report	467 (89.1)	258 (89.9)	0.755	498 (83.6)	305 (91.0)	**0.006**
Pharmacists to report	472 (90.4)	261(90.9)	0.610	531 (89.1)	311 (92.8)	**0.030**

ADR: Adverse Drug Reaction, P value from Pearson Chi square, NPC- National Pharmacovigilance Centre, SSZPC- South-South Zonal Pharmacovigilance Centre. HCPs: HealthCare Professional

Table 4: Attitude to ADR reporting of HealthCare Professionals between intervention and control groups, before and after the intervention, n (%)

	Pre-intervention			Post Intervention		
Attitude to ADR reporting items	**Intervention (n=524)**	**Control (n=287)**	**p-value**	**Intervention (n=596)**	**Control (n=335)**	**p-value**
Belief that all ADRs should be reported	481 (91.8)	262 (91.7)	0.191	520 (87.2)	306 (91.3)	0.051
No difficulty in determining occurrence of ADRs	303 (57.8)	153 (53.3)	0.671	346 (58.1)	212 (63.3)	**0.003**
Reporting when unsure if ADR has occurred	388 (74.0)	203 (70.7)	0.703	408 (68.5)	203 (60.6)	**<0.001**
Reporting when not sure it will make a difference	370 (70.6)	189 (65.9)	0.264	337 (56.5)	239 (71.3)	**<0.001**
Not expecting to receive incentives for reporting	375 (71.6)	239 (83.3)	**0.001**	402 (61.1)	264 (78.8)	**<0.001**
Professional obligation to report	482 (92.0)	258 (89.9)	0.787	511 (85.7)	312 (93.1)	**0.005**
Reporting should be made mandatory	468 (89.3)	260 (90.6)	0.335	525 (88.1)	307 (91.6)	**0.013**
ADR reporting does not put career at risk	479 (91.4)	260 (90.6)	0.510	505 (84.7)	310 (92.5)	**0.002**
ADR reporting should not be for publishing only	461 (88.0)	260 (90.6)	0.290	462 (77.5)	317 (94.6)	**<0.001**

Health care professionals practice of adverse drug reaction reporting (Table 5)
The proportion of HCPs in the intervention group who had received training in ADR reporting increased statistically compared with those in the control group after the intervention (24.3% vs. 11.6%, p=<0.001). As well, the proportion who had ever observed an ADR increased significantly (82% vs 73.4%, p=0.001) in the HCPs from the intervention group. Use of the adverse drug reaction reporting form was significantly different between the control and intervention groups from both the pre- and post-intervention questionnaire.

Of the respondents who had ever reported an ADR using the national ADR reporting form, 18.6% were able to access the form in the intervention group compared with 9.9% in the control (p=0.02). ADR reporting in the intervention group was also higher 29.8% vs. 18.7%, (p=<0.001).

Table 5: Practice of Pharmacovigilance of HealthCare Professionals between intervention and control groups, before and after the intervention, n (%)

Practice items	Pre-intervention			Post Intervention		
	Intervention (n=524)	Control (n=287)	p-value	Intervention (n=596)	Control (n=335)	p value
Training on ADR	84 (16.0)	43 (15.0)	0.821	145 (24.3)	39 (11.6)	<0.001
Observed ADR	423 (80.7)	240 (83.6)	0.222	489 (82.0)	246 (73.4)	0.001
Reported ADR	166 (31.7)	78 (27.2)	0.394	188 (31.5)	91 (27.2)	0.256
Use of the national reporting form*	80 (49.4)	18 (23.4)	<0.001	77 (41.0)	18 (19.8)	<0.001
Easy access of ADR forms*	49 (29.5)	10 (12.8)	0.001	35 (18.6)	9 (9.9)	0.022
Easy reporting with the ADR form*	84 (50.6)	16 (20.5)	<0.001	56 (29.8)	17 (18.7)	<0.001
Easy mode of returning ADR forms*	16 (9.6)	3 (3.8)	0.003	34 (18.1)	6 (6.6)	<0.001

* The number of respondents who had reported an ADR is the denominator. ADR: Adverse Drug Reaction. P value from Pearson Chi square.

Discussion

This study evaluated the effect of an educational intervention and reminders in improving the Knowledge, Attitude and Practice of health care professionals (HCPs) in the South-South zone of Nigeria towards pharmacovigilance in order to ultimately improve the number of reports from the zone. This was the first study to our knowledge in this resource constrained setting to utilize a method of first a didactic lecture followed by monthly SMS reinforcement reminders for 12 months on the necessity of reporting ADRs. The short messaging system was utilized due to its accessibility and the high mobile phone penetration in Nigeria. The healthcare professionals showed improvement in some of the knowledge items, the perception and practice of pharmacovigilance. We also believe this method had an advantage of reaching a high proportion of health care professionals as the intervention was delivered both at the level of the institution and to consenting health care workers which would have also allowed for dissemination between the members of the same institution [36,37]. Furthermore, the randomized nature of the study allowed for comparison of the effect of the intervention with centres that had not received the intervention and this further strengthened the study Single institutional pre-post studies had also suggested the positive impact of mixed educational strategies [16,17].

There was a difference in the knowledge of the health professionals after the intervention especially in the items relating to the types of adverse drug reactions, this is important as recognition of the various types of ADRs is the first step in ensuring that reports may ensue from such cases [38]. Under-recognition has been a major drawback in adverse drug reaction reporting worldwide [3], therefore this improvement is very important in tackling this issue. The knowledge of the scope of pharmacovigilance also improved after the intervention in this study as seen in a similar study [39]. This is notable as awareness of the scope will increase reporting of such cases and can stimulate targeted public health intervention as a systematic review had also suggested that up to 50% of those sampled felt all medicines available in the market were safe [40]. Furthermore, the knowledge that cases of medication errors, drugs misused and abused should be reported are important considerations of public health importance especially as health professionals are usually reluctant in reporting such cases [41]. In effect, understanding that such cases are to be reported constitutes a significant gain to the participating health professionals.

We also noted an improvement in the awareness of existence of the South-South Zonal Pharmacovigilance Centre following the intervention in this study. This is a key finding as this regional centre had been newly created but as seen in the baseline results, the awareness of its existence was low initially. Regionalization of ADR reporting centers has been shown to improve the number of reports and timeliness of those reports [42]. Therefore, increasing the awareness of this centre was one of the key components of the educational intervention in this study and this may be the initial step in improving reports. Similarly there was an increased awareness of the ADR reporting form from baseline. A key determinant in reporting with the national form is the awareness of its existence as previous studies have shown that although health professionals observe ADRs, they may report using other routine hospital processes and most ADRs go unreported [9,38,43].

In this study, the respondents in the intervention group still believed they should report even when unsure an ADR has occurred. This positive attitude may sustain the culture of reporting as uncertainty of ADR occurrence has been suggested as a probable cause of under-reporting [38]. Other studies have also suggested attitudinal challenges contribute to underreporting [40,43,44]. However, we note the change in the positive attitudes in the control

group. This may be because the respondents in this group were exposed to the baseline questionnaire which may have stimulated interest in ADR reporting and this may have accounted for these changes. Also we could not rule out repeated lectures on pharmacovigilance at those sites in the control arm due to the presence of enthusiastic healthcare professionals encountered during the baseline assessment. Attitudinal changes which have been described as key components towards improving the behavior of health professionals [23,37] are quite complex to evaluate as studies have suggested that several factors are responsible for behavioral changes [45].

To attain the goal of increasing ADR reports at the National Pharmacovigilance centre, it is recommended that the national ADR form be used in reporting ADRs. This was emphasized during the intervention and subsequent reminders sent to the health care professionals. We observed an increase in the proportions of respondents who recalled having ever used the form to report rather than other modes of reporting. This finding supports the possible influence of long term reinforcement as seen in this study with the 12 month long monthly SMS reminders as well as education on improving ADR reports and reiterates that frequent continuous medical education and possibly the use of mobile technology may serve as a means to improving the practice of pharmacovigilance [12,16,23]. The use of the SMS in this study served to buttress the need to tailor interventions to the respondents in a manner that could be reproducible and would not require excessive funding to prosecute in future.

Again, the cumbersome processes of accessing and returning ADR reporting forms are factors that have been linked to poor reporting rates [12,46]. Therefore, location and phone numbers of the local pharmacovigilance centers were made available to the health care professionals in order to observe if this would ease the process of access or return. {#It was observed that the respondents still had some difficulty accessing, reporting with the form and returning the forms, unlike similar studies that showed improvement in HCPs understanding of the reporting processes [15,47]. This suggests that the pharmacovigilance systems at the institutions in this study may need to be frequently evaluated and strengthened [48,49].

Limitations: The control arm in this study may have had some external training on pharmacovigilance either from the NPC or the local pharmacovigilance committee pharmacovigilance activities. We also could not evaluate the impact of the intervention in the respondents who participated in the first survey due to the logistics of accessing the HCPs and the possibility of a very high drop- out rate. However, the repeat cross-sectional design has also been shown to give comparable results when applied in same group[50] and we did not expect the population to change much during the course of the study despite the dynamics of the teaching hospital setting. We could also not rule out contamination in this study despite all attempts to minimize it. Some respondents failed to answer all questions; this may be a reflection of poor knowledge of those HCPs and will require further evaluation. We also did not address the influence of factors such as specialty, area of practice, gender on the intervention results. Future interventions will target various cadres, specialties in order to improve ADR awareness and practice. Again, we could not ascertain if the SMS were delivered to all those who participated or if they read them. The Nigerian health sector also underwent major industrial actions that may have impacted on the results.

Conclusion

There was an improvement in the knowledge and practice of pharmacovigilance and ADR reporting by the respondents following the educational intervention. However, attitudinal changes may require further targeted interventional strategies. SMS reminders as a reinforcement tool appear to have been useful in this setting. Further, an improvement in the reporting process may also improve the HCPs practice of pharmacovigilance.

Acknowledgement:

The authors thank the Chief Medical Directors of the various institutions visited as well as the members of the pharmacovigilance committees, units and staff of the hospitals. We are also grateful to the Director General of the National Agency for Food Drugs Administration and Control (NAFDAC) HQ, Abuja and the South – South Zonal Staff for their kind assistance in carrying out this work.

Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests:

The Authors declares that there is no conflict of interest.

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Educational Intervention to improve the Knowledge, attitude and Practice of Health Care Professionals regarding pharmacovigilance in South-South Nigeria.

Supplemental Information 1: Monthly text messages sent to the health care professionals in the intervention arm of the South- South Zone of Nigeria over 12 months.

1. Drug Rxn SSZPC
   Pharmacovigilance
   Please report all adverse drug reaction cases using YELLOW FORMS to the Drug Information Center in OPD pharmacy.
   Or call Pharm in charge on 08027640022.
   Or scan & email the report to zpcsouthsouth@gmail.com. 09092474258
2. Drug Rxn SSZPC
   Pharmacovigilance
   Please report all adverse drug reaction cases using YELLOW FORMS to the Drug Information Center in OPD pharmacy.
   Or call Pharm in charge on 08027640022.
   Or scan & email the report to zpcsouthsouth@gmail.com. 09092474258
3. Title: Drug RXN
   Pharmacovigilance: Report ALL ADVERSE DRUG REACTIONS with NAFDAC FORMS to DPIC/COPD pharmacy, or call 08033733534, 08037075435 or email ZPC at zpcsouthsouth@gmail.com

4. Drug RXN
   Adverse drug reactions are NOXIOUS unintended response to drugs used at normal doses. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
   Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

5. Drug RXN
   Adverse drug reactions are NOXIOUS unintended response to drugs used at normal doses. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
   Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

6. Drug RXN
   Adverse drug reactions can be known or new, could be delayed for a long time or occur at the end of use. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
   Or email it to zpcsouthsouth@gmail.com. or call 08037075435.
7. Drug Rxn
   There is no penalties for reporting an adverse drug reaction. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022.Or email it to zpcsouthsouth@gmail.com. or call 08037075435.
8. Drug Rxn
   Reporting Drug reactions aids patient safety. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022.Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

9. Drug Rxn
   Season greetings, ALL adverse drug reactions should be reported. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
10. Drug Rxn
    Season greetings, ALL adverse drug reactions should be reported. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022. Or email it to zpcsouthsouth@gmail.com. or call 08037075435.
11. Drug Rxn
    It takes 10 minutes to report DRUG REACTIONS. ALL suspected cases should be reported to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022 08037075435. Or email it to zpcsouthsouth@gmail.com
12. Drug Rxn
    Call the Pharmacovigilance Unit on 08027640022 or 08037075435 to report ALL suspected adverse drug reactions in the hospital OR use the NAFDAC Yellow Form. Or email it to zpcsouthsouth@gmail.com

CHAPTER 6:

IMPACT OF AN EDUCATIONAL INTERVENTION ON ADVERSE DRUG REACTION REPORTING IN TERTIARY HOSPITALS IN SOUTH-SOUTH NIGERIA.

Chapter 6 Impact of an educational intervention on adverse drug reaction reporting in tertiary hospitals in South-South Nigeria.

Opadeyi AO, Fourrier-Réglat A. Isah AO. Impact of an educational intervention on adverse drug reaction reporting in tertiary hospitals in South-South Nigeria.

Submitted to West African Journal of Medicine- December 2018

Abstract

Under-reporting of Adverse Drug Reactions (ADRs) has been shown to be a major hindrance to the growth of pharmacovigilance worldwide. Nigeria is yet to achieve the internationally recommended number of reports.

Objectives: To evaluate the impact of an educational lecture followed by repeated text messages via the Short Messaging System (SMS) on ADR reporting as determined by the number of reports and the quality of reporting.

Methods: Six randomly selected teaching hospitals in the South-South zone of Nigeria were randomised in 1:1 ratio into intervention and control groups. The intervention consisted of delivering an educational seminar and sending monthly texts message reinforcements via SMS over 12 months. According to the reports sent to the local pharmacovigilance centres of the hospitals. The number and quality of ADR reports from each teaching hospital over the 12 months before and after the intervention were recorded and described

Results: A total of 4912 healthcare professionals were eligible to participate in the study (3099 in the intervention and 1813 in the control) and about a third participated in the intervention held between January and March 2016. The number of ADRs reports increased from 57(85.1%) in the pre-intervention period (from January 1st 2015) to 75(93.8%) in the post intervention period. The proportion of valid reports also increased from 84.2% to 86.7%, in the intervention arm. However, the proportion of serious ADRs decreased slightly from 45.6% to 44%. The ADR report form fields that improved post intervention were suspected drug details and reporter details.

Conclusion: The educational intervention and SMS reminders appeared to have increased the absolute numbers and quality of reports. There is need to consolidate these findings and broaden the scope of interventions in the area of pharmacovigilance.

Key words: Educational intervention, adverse drug reaction, healthcare professionals, SMS reminders, Nigeria

Key points

The use of targeted multifaceted interventional strategies improved the reporting of adverse drug reactions in a resource constrained environment.

The morbidity mix and ethnic peculiarities of the country may have impacted on the profile of adverse drug reactions obtained in the study.

Continuous healthcare professional engagement may be key towards improving the pharmacovigilance system.

Background

The World Health Organization defines an adverse drug reaction (ADR) as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the diagnosis or therapy of disease, or for the modification of physiological function [1]. It is a global problem and a significant cause of hospital admissions contributing to increased morbidity and mortality of the population [2–4]. Although this burden has not been well quantified in Nigeria, it is however bound to be considerable [5]. There is need for constant surveillance of a medicinal product regardless of the number of years in the market due to the possibility of development of ADRs at any point in time and only a high index of suspicion will ensure that this is detected [6].

Spontaneous reporting of ADRs to medicines remains the primary reporting modality despite other active surveillance measures to detect less rare adverse reactions [7]. It has however been hindered by under-reporting by health care professionals as evident in a systematic review where the median under-reporting rate was 94% [8]. Furthermore, an analysis of ADR reports in the Vigibase™ over a decade revealed that low to lower middle income countries had lower reporting rates than the high income countries [9]. This reflects the possible impact of an organised pharmacovigilance system in the high income countries. Identification and reporting of safety issues is low in most parts of Africa although this is being tackled within growing pharmacovigilance systems and identification of key intervention areas [10].

Nigeria is also associated with poor reporting rates despite an increasing number of reports in the national database [11]. This could be attributed to lack of awareness of the reporting system, cumbersome reporting process, feeling that reporting will not make a difference and uncertainty on what to report [12–14]. This is not different from what was observed in other parts of the world [15]. There have been few studies describing the profile of adverse drug reactions in Nigerians despite the number of reports in the database[11,16,17].

Interventional strategies that have been designed to improve adverse drug reaction reporting include provision of drug safety bulletins, inclusion of yellow forms in prescription pads, lectures, personal briefings, repeated emails or short text messages, telephone calls, workshops, web based software as well as provision of incentives to reporters [18–23]. These have targeted different cadres of health care professionals and patients and have had varying degrees of success. It has however been demonstrated that continuous training and education remains key to ensuring the sustainability of any intervention program [24].

Despite different preliminary studies that have evaluated the factors associated with adverse drug reaction reporting in single health facilities in Nigeria, there have been no studies evaluating the effect of a multi-dimensional and targeted intervention on adverse drug reaction reporting in a geographical zone in Nigeria. It is imperative to apply measures that are easy to deploy in a setting [25] when designing an educational intervention. Furthermore, a combined approach has been found useful in improving outcomes [26]. The poor response to a questionnaire based study using emails as a delivery mode in the country [20] suggests that alternate methods of delivering reminders were needed. Thus the use of the mobile Short Messaging System (SMS) in communicating with the health care professional may be more effective since most Nigerians have a mobile telephone device. The design and effectiveness of an educational intervention in changing behaviour of healthcare workers has been discussed in various studies[25,27,28]. The positive impact of a

mixed effect of continuous medical education and other forms of intervention in changing health care workers behaviour has also been described[26]. This study set out to evaluate the effect of an educational intervention with repeated SMS reinforcements to health care professionals (doctors, nurses and pharmacists) in the South-South zone of Nigeria on the number, quality as well as the profile of adverse drug reactions reports.

Methods

Study setting and design:

The study was conducted in teaching hospitals which are tertiary care centres in the South-South geopolitical zone of Nigeria, located in the coastal region of Nigeria and home to about 21 million residents (National census 2006). The zone is comprised of 6 states – Akwa- Ibom, Bayelsa, Cross-Rivers, Delta, Edo and Rivers State. All hospitals have a complement of doctors, pharmacists and nurses to cater for the health needs of the populace.

Selection of facilities and randomization

A sampling frame of all Tertiary hospitals in the zone was obtained to include teaching hospitals, Federal Medical Centers as well as Specialist hospitals that have a particular focus for treatment such as neuro-psychiatric hospitals. Teaching hospitals were selected for the study as they provided the widest access to both patient and health care professionals complement and were also in a position to train different cadres of undergraduates and post graduates. There were eight teaching hospitals in the zone and then 6 teaching hospitals were randomly selected using a table of random numbers with one teaching hospital representing a state and three hospitals to receive the intervention. Other tertiary hospitals in the zone were excluded from the study as they were not teaching hospitals. To be included in the study, ethical and institutional approval was required from the ethics and research committee and Chief Medical Director of the institution respectively. Six institutions were included into the study namely: University of Benin Teaching Hospital Benin-City, Edo State, (UBTH); Delta State University Teaching Hospital Oghara, Delta State (DELSUTH); Niger Delta University Teaching Hospital Okolobri, Bayelsa State, (NDUTH); University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, (UPTH); University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State (UUTH) and University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH). Three institutions were randomized to receive the intervention prior to commencement of the study following ethical and institutional approval.

Educational intervention

Interventions

An intervention was implemented in the following hospitals: University of Benin Teaching Hospital Benin-City, Edo State, (UBTH); University of Uyo Teaching Hospital, Uyo, Akwa- Ibom State (UUTH) and University of Calabar Teaching Hospital, Calabar Cross-River State, (UCTH).

Educational intervention

The design here consisted of an active intervention with a seminar presentation followed by a passive year-long reinforcement with monthly delivery of text messages. It included an hour long seminar delivered to the health workers at the various institutions in the intervention arm of the study at specially organised meetings. The seminar focused on the scope and aims of pharmacovigilance [26]. All post-registration health care professionals working in the selected teaching hospitals were eligible to be recruited into the study if they consented to participate in the study. The HCP gave written consent before filling a questionnaire and indicated their willingness for future contacts. We also allowed for those

who attended the seminar to receive text messages. House-officers, pharmacy interns and students were excluded from the study as they were undergoing supervised training at the time.

The seminar was an hour-long presentation delivered to the health care professionals at specially organised meetings. It was in two parts - firstly the scope and aims of pharmacovigilance were outlined using the WHO documents on pharmacovigilance, the definitions of the different key items of the ADRs [1,29,30]. The definitions of the different key items of the ADRs,[31,32] then the historical aspect of ADRs and relevant history of pharmacovigilance in Nigeria was described. The number of reports presently in the Nigerian database with the system organ classification and pharmacological classification was made known.

Secondly emphasis was laid on ADR reporting, types of reports, reasons to report, how to report and other reporting modalities. The submission processes and consequences as well as frequently asked questions in ADR reporting were presented. Finally, an algorithm of the ADR reporting process was explained and the contacts of relevant persons and institutions listed. Posters and handbills regarding pharmacovigilance from the National Pharmacovigilance Centre were shared after the lecture. Short text messages reminding the HCP to report all ADRs and the contacts details of the local pharmacovigilance centre personnel were sent to the health care professionals in the institutions monthly over 12 months after the educational intervention. The text messages had the title- Drug RXN and then a reminder to report ADRs as well as how to access the national ADR reporting form "Yellow Form" and contact numbers of the local pharmacovigilance contact persons. Supplemental information 1

The educational seminar took place between January 2016 and March 2016 in the three intervention hospitals. The presentation was made one of the researchers (AOO). The participants in the other three hospitals received news from the national pharmacovigilance centre as usual and they could also report ADRs to their local pharmacovigilance centres

Data sources

The ADR reports that had been submitted to each of the local pharmacovigilance centres in all hospitals over 12 calendar months preceding the intervention starting from 1st January 2015 and all ADR reports obtained subsequently over 12 months after the intervention submitted to the local pharmacovigilance centre of each institution were evaluated and reported in this study. The absolute numbers were recorded per institution.

Outcomes

The number and type of ADRs reports submitted to the pharmacovigilance centre or designated co-ordinator were used as the outcome measure in this study. The quality of the ADR reports was assessed by ascertaining the completeness of the fields in the Nigeria national ADR reporting form in each report.

Data analysis

All ADR reports during the period were assessed to establish if all the elements in the form were filled and if the requirements of a valid report were met. A valid report is that which meets the WHO criteria for minimum reports [33].ADRs were also classified as serious and

non serious based on the International Conference on Harmonisation guidelines (ICH E2A) [33]. A serious ADR was defined as any untoward medical occurrence at any dose that results in hospitalisation or prolongation of existing hospitalisation, persistent or significant disability, results in death, is life threatening or results in a birth defect or congenital anomaly. Medical events in which an intervention was or may have been required to prevent any of the afore-mentioned outcomes that fall under the classification of serious ADRs were also regarded as serious ADRs. All ADR reports were forwarded to the National Pharmacovigilance Centre.

In reporting the ADRs, the Medical Dictionary for Regulatory Activities MedDRA® terminology Version 20 was utilised in coding the ADR with the system organ classification (SOC) described for each reaction "MedDRA® is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)". (MedDRA trademark is owned by IFPMA on behalf of ICH). The outcome of the reaction was classified into recovery, permanent disability, life threatening or death.

The Anatomic Therapeutic Chemical classification (ATC) was used to classify the suspected medicines using the therapeutic levels I, II and V classification as well as the ATC codes [34]. Causality assessments were carried out using the WHO causality assessment system and the Naranjo causality assessment algorithm[35,36]. The researchers as well as trained staff at the South-South Zonal Pharmacovigilance Centre conducted the assessments.

Statistical Analysis

The intervention seminar was delivered at the level of the hospital and all eligible healthcare professionals working in the intervention institutions were invited to receive the intervention. Additionally seminars were delivered in departments/units to further improve the coverage. The results are expressed as frequencies, proportions and percentages and means(SD) as appropriate. Microsoft Excel 2007 and the statistical package for social sciences SPSS version 21 for windows were used to analyse the data.

Ethical approval

Ethical and institutional approval was obtained from the ethics and research committees as well as the Management of all the hospitals respectively prior to commencement of the study. Delta State University Teaching Hospital Oghara: DELSUTH/HREC/2015/024, Niger Delta University Teaching Hospital, Okolobri: NDUTH/REC/0005/2015, University of Benin Teaching Hospital Benin-City: UBTH:ADM/E22/2/VOL.VII/1245, University of Calabar Teaching Hospital, Calabar: UCTH/HREC/33/360, University of Port Harcourt Teaching Hospital, Port Harcourt: UPTH/ADM/90/S.II/VOL.X/668 and University of Uyo Teaching Hospital, Uyo: UUTH/AD/S/96/VOL.XIV/357. Participants had given a written informed consent to participate in the study and also supplied their phone numbers to allow for contact.

Results

A total of six randomly selected teaching hospitals participated in this study. The three hospitals that received the intervention had a bed complement of 1810 beds and had approximately 3099 post registration healthcare professionals (doctors 43%, nurses 54% and pharmacists 3%) working in them at the commencement of the study. The three non-intervention hospitals had a bed complement of 1180 beds and had 1813 post-registration healthcare professionals (doctors 41%, nurses 55% and pharmacists 4%) working in them also at the same time.

ADR reports including patient's demographics

Intervention hospitals

Over the pre-intervention period, an overall number of 57 ADR reports were found in the pharmacovigilance databases of the 3 intervention hospitals. The proportion of valid ADR reports (defined as an ADR report meeting the WHO minimum reporting criteria) was 84.2%. Over the post- intervention period, the number of reports increased to 75 reflecting a 31.6% increase from the pre-intervention period. The proportion of valid ADRs also increased to 86.7% but this was not statistically significant (χ^2=0.159, p=0.69).

Between the pre and post intervention period, the sex-ratio (F/M) of the ADR reports varied with more females than males 3.8:1 pre-intervention and 1.9:1 post intervention. The mean age (SD) of the patients with adverse drug reactions was 40.3(19.7) years pre-intervention to 38.0(20.0) years post intervention and those aged 18 to 64years were mostly affected. This was not significant (t=0.664, p=.508). More reports were received in the first quarter post -intervention. (Table 1)

Non-interventional hospitals

Over the pre-intervention period, 10 ADR reports were found in the local pharmacovigilance databases of these hospitals and 80% of them were valid. The total number of ADR reports decreased to 5 reports in the post intervention period and 4 (80%) were valid. The age group most commonly affected were those aged 18-64 years in the pre and post intervention period. (Table 1)

Table 1: Characteristics of adverse drug reactions reports (pre and post intervention) from the six teaching hospitals in the South-South zone of Nigeria.

Characteristic	Intervention hospitals			Non-Intervention hospitals		
	Pre-Intervention (n=57)	Post - Intervention (n=75)	p-value	Pre-Intervention (n=10)	Post – Intervention (n=5)	p-value
Mean age(SD) years	40.3 (19.7)	38.0 (20.)	0.508	40.9 (21.9)	39.4(15.27)	0.894
Age group						
0-17years	4 (7.0)	11 (14.7)		0	0	
18-64years	44 (77.2)	57 (76)		9 (90)	5 (100)	
65 and above	6 (10.5)	5 (6.7)		0	0	
Adult	1 (1.8)	0		0	0	
Not stated	2 (3.5)	2 (2.7)		1 (10)	0	
Sex (%)						
Male	12 (21.1)	26 (35.1)		8 (80.0)	1 (20.0)	
Female	45 (78.9)	48 (64.9)	0.085	2 (20.0)	4 (80.0)	0.089
Number of reports per quarter						
First quarter	13 (24.5)	34 (45.3)		5(50.0)	1 (20.0)	
Second quarter	10(18.9)	22 (29.3)		1 (10.0)	1(20.0)	
Third quarter	7(13.2)	12(16.0)		3 (30.0)	1 (20.0)	
Fourth quarter	23(43.4)	7(9.3)	<0.00	1(10.0)	2(40.0)	0.999
Valid ADRs	48 (84.2)	65 (86.7)	0.804	8 (80)	4 (80)	1.000

ADR: Adverse Drug Reaction, SD: Standard Deviation

Profile of the adverse drug reactions (pre and post intervention)

Intervention hospitals

Skin and subcutaneous tissue disorders were the highest ADR presentations pre and post-intervention as shown by the MedDRA® SOCs of the ADR reports. Post intervention, there were also more ADR reports relating to general disorders and administration site conditions, (30.7%) and psychiatric disorders (21.3%) and this was significant for psychiatry disorders (U=1867, p=0.02). Table 2.

Pre-intervention anti-infectives medicines for systemic use accounted for 22(38.6%) of all reports. Of this, 54.5% were antivirals for systemic use and 45.5% were antibacterials. All the antiparasitic products reported were antimalarials and 80% of the five cardiovascular system medicines were agents acting on the renin-angiotensin system (Figure 1). During this period, there was a case of suspected haemolytic anaemia following ingestion of an herbal medicine (active ingredients unknown), two cases of medication errors (wrong drug dispensed and administered- (carbamazepine instead of metformin, and chlorpromazine instead of donepezil). There was also a case of a patient who used multiple NSAIDs resulting in upper gastrointestinal bleeding.

Post intervention, of the 41 anti-infective medicines for systemic use, antiviral for systemic use accounted for 65.8%, antibacterials-(22%), antimycotics (2%), antimycobacterials (4.9%) vaccines (4.9%). Again, only antimalarials were the only suspected antiparasitic medicines and all eight (8) implicated cardiovascular system medicines were agents acting on the renin-angiotensin system. Furthermore, ADRs following the use of vaccines (2),

diagnostic agents (1), ophthalmologicals (1) use of multiple medicines including herbal supplements, as well as a case of carbon monoxide poisoning were reported (Figure 1).

Non intervention hospitals

Skin and subcutaneous tissue disorders were also the highest SOCs for ADR reported in the pre and post intervention period. Other SOCs encountered were gastrointestinal disorders and psychiatry disorders. Table 2. Medicines acting on the nervous system followed by anti-infectives for systemic use (ATC level 1) were the most implicated group of medicines (Figure 1).

Table 2: System organ classification (MedDRA) of adverse drug reactions reported pre and post intervention in the six teaching hospitals in South-South Nigeria.++

Characteristic	Intervention hospitals			Non-intervention hospitals		
	Pre-Intervention n=57(%)	Post – Intervention n=75(%)	p- value#	Pre-Intervention (n=10)	Post – Intervention (n=5)	p- value#
Skin and subcutaneous tissue disorders	29(50.9)	39(52)	0.857	7(70)	4(80)	0.859
Nervous system disorders	22(38.6)	29(38.7)	0.650	0	1(20)	0.594
Gastrointestinal disorders	20(35.1)	24(32)	0.741	0	0	0
General disorders and administration site conditions	13(22.8)	23(30.7)	0.862	3(30)	1(20)	0.768
Psychiatric disorders	2(3.5)	16(21.3)	0.02	4(40)	1(20)	0.679
Respiratory, thoracic and mediastinal disorders	6(10.5)	7(9.3)	0.919	2(20)	0	1.000
Eye disorders	11(20.2)	5(6.7)	0.047	1(10)	0	0.768
Cardiac disorders	2(3.5)	4(5.3)	0.619	0	0	0
Metabolism and nutrition disorders	0	5(6.7)	0.078	0	0	0
Musculoskeletal and connective tissue disorders	3(5.3)	3(4)	0.731	0	0	0
Renal and urinary disorders	3(5.3)	2(2.7)	0.441	0	0	0
Ear and labyrinth disorders	5(8.8)	2(2.7)	0.769	0	0	0
Investigations	2(3.5)	1(1.3)	0.781	1(10)	0	0.768
Infections and infestations	0	1(1.3)	0.383	0	0	0
Hepatobiliary disorders	1(1.8)	1(1.3)	0.845	1(10)	0	0.768
Injury, poisoning and procedural complications	3(5.3)	0	0.403	0	0	0
Reproductive system and breast disorders	1(1.8)	0	0.251	0	0	0
Surgical and medical procedures	1(1.8)	0	0.251	0	0	0
Vascular disorders	2(3.5)	0	0.103	0	0	0

++ There were multiple ADRs and SOCs reported for each patient #-mann Whitney U test statistic applied.

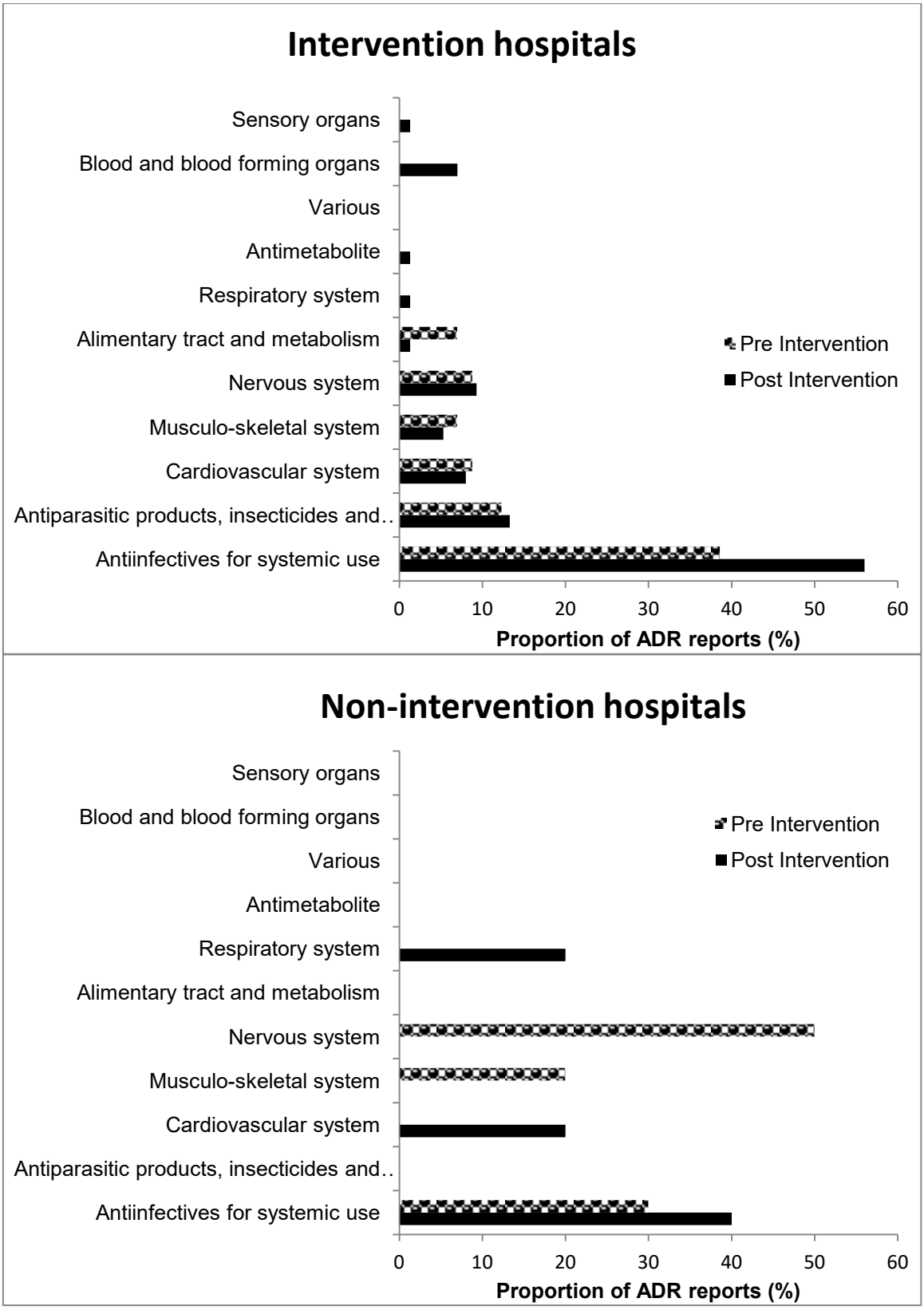

Fig 1: Anatomic Therapeutic Chemical (ATC) classification of suspected medicines causing adverse drug reactions (ADR) in six teaching hospitals in South-South Nigeria. (Pre and post intervention).

Evaluating the ADRs from the various medicine classes in all six hospitals, tramadol hydrochloride was the most implicated single agent in 6 patients, and it was associated with reactions in the following SOCs -general disorders and administration site conditions (5), skin and subcutaneous tissue disorders(3), respiratory, thoracic and mediastinal disorders(2). Others were musculoskeletal and connective tissue disorders, gastrointestinal and nervous system disorders (3).

However, a combination of lamivudine, zidovudine and nevirapine was the most commonly implicated combination therapy in ADRs reviewed with -general disorders and administration site conditions(9) and gastrointestinal disorders(6) being the most commonly associated SOCs. Artesunate –mefloquine combination of the artemisinin combination derivatives was the most commonly implicated antimalarial medicine (5) and it was mostly associated with nervous systems disorders SOC. Ramipril and lisinopril were the most suspected cardiovascular medicines causing adverse reactions and they were associated with reports of angioedema (2), lip, tongue and eye swelling (6).The ADRs from other anti-infectives, antiparasitic agents, cardiovascular medicines as well as from analgesics with their associated SOCs are as noted in Supplemental Information II.

Outcome of the adverse reactions:

Intervention hospitals

As observed in the 57 ADR reports received pre-intervention, full recovery was recorded in 54%, partial recovery-28%, permanent disability- 1.8%, life threatening-10.5%, no deaths and indeterminate outcome-5%. Post intervention, of the 75 ADR reports, 37% recovered fully, 38.7% had partial recovery, permanent disability-4%, life threatening-9.3%, death -2% and indeterminate outcome in 8%.

Non-intervention hospitals

Pre and post intervention, more cases recovered fully 40% and 30% respectively. Also 50% in the pre-intervention phase, had life threatening conditions and there was one fatality.

Causality assessment

Most of the ADRs were possible after applying both the WHO causality assessment system and the Naranjo causality algorithm. There were very few cases of certain ADR and none of definite. Table 3.

Table 3: WHO and Naranjo algorithm causality assessments of the ADRs from the South- South- South zone of Nigeria pre and post an educational intervention and reinforcements;

Scale item	Intervention			Non-intervention hospitals		
WHO scale items	**Pre-Intervention n=57(%)**	**Post–Intervention n n=75(%)**	**p value***	**Pre-Intervention n=10**	**Post – Intervention n=5**	**p value***
Certain	3(5.3)	2(2.7)	0.544	0	0	0.269
Probable	11(19.3)	9(12.0)		1	1	
Possible	32(56.1)	50(66.7)		9	3	
Unlikely	3(5.3)	7(9.3)		0	0	
Conditional	0	1(1.3)		0	0	
Unassessable	8(14.0)	7(9.3)		0	1	
Naranjo scale items						
Definite	0	0	0.028	0	0	0.099
Probable	9(15.8)	7(9.4)		0	1	
Possible	38(66.7)	64(85.3)		10	3	
Doubtful	10(17.5)	4(5.3)		0	1	

**Chi-square analysis*

ADR Reports involving children and adolescents:

There were four ADR reports involving children and adolescents in the pre-intervention phase and all four ADR reports were serious. The suspected medicines were all antibacterials for systemic use. There were 11 reports in the post intervention phase, eight were serious ADRs, and one was fatal due to Steven Johnsons Syndrome, the causative agent not having been determined. Suspected drug classes were antibacterials for systemic use-1, antiprotozoals- 3, vaccines-2, antiepileptics, antivirals for systemic use, nasal preparations, drugs for functional gastrointestinal disorders and multiple drugs used by a patient. There was no report regarding children and adolescents in the non- intervention hospitals pre or post.

Reports of serious ADR:

Intervention hospitals

Pre intervention period, the proportion of serious ADRs was 45.6%. Post intervention, it was 44% of all reported ADRs (not significant, χ^2=0.034, p=0.853). There were two recorded fatalities in the post intervention phase following the use of tramadol and multiple medicines. No fatality was recorded in the pre-intervention phase.

Pre- intervention, antinfectives for systemic use was the group most associated with serious ADRs 10 38.5%). Of which antibacterials (70%) were the highest contributors. Other notable groups include agents acting on the renin-angiotensin system -11.5%, psycholeptics -11.5%. Post intervention, anti-infectives for systemic use remained the highest causative group for serious ADRs 10 (30.3%). Of which, antivirals for systemic use (60%) were the highest contributors. Antimalarials especially artemisinin and derivatives combinations -17.6%, angiotensin converting enzymes plain -14.7% and Antiinflammatory and antirheumatic products, non steroidal medicines -11.8% were also implicated in serious ADRs.

Some notable serious ADRs seen include sudden bilateral sensorineural deafness following intravenous moxifloxacin use, anaphylactoid reaction with angioedema following oral intake of an over the counter Vitamin B1/B12/B6 supplement.

Non-intervention hospitals

Pre intervention period, all ten reported ADRs were serious, Post intervention there was only 1 serious case was reported from the control arm which was a fatality and had multiple medicines implicated. There was no fatality reported in the pre-intervention phase. Tramadol (an opioid analgesic) was the singular most suspected medicine in 4 patients with serious ADRs emanating from a single centre. Antiinflammatory and antirheumatic products non- steroidal medicines (2) also contributed to serious ADRs.

Reporting centres and source of reports:

Intervention hospitals

Pre intervention period, one of the centres had no ADR report in its database but all centres had ADR reports after the intervention. Pre intervention, of the 57 ADR reports found in the database, medical doctors submitted 57.9%, pharmacists 35.1%, and 7.0% had no reporter details filled. Post intervention, of the 75 ADR reports submitted, 30.1% were from doctors, pharmacists 68%, and no reporter details were filled in 1.3%. This was statistically significant χ^2=18.21, p=<0.001. No nurse in these centres reported an ADR report during the study. Doctors submitted more valid ADR reports in the pre-intervention period than pharmacists (59.6% to 27.9%). However, in the post intervention period, pharmacists submitted more valid ADRs and this was significant. (χ^2=11.58, p=0.001).

Pre-intervention, of the 26 cases of serious ADRs reported, 84.6% were from doctors, pharmacists 11.5%, reporter not stated 3.8%. Post intervention, of the 33 cases of serious ADRs reported 57.6% were made by doctors, and 42.4% by pharmacists. This was also significant (χ^2= (18.21, p=<0.001)

Non intervention hospital

Two hospitals had ADR reports at the pre-intervention phase and all three hospitals had ADR reports at the completion of the study. All 10 ADR reports obtained in the pre-intervention period, were serious ADRs and 50% were from nurses, doctors- 20% and pharmacists 20% while 10% had no reporter details. Post intervention period, 80% of the ADR reports were made by pharmacists and the only serious ADR reported was by a doctor.

Completeness of the National Pharmacovigilance Centre adverse drug reaction reporting form

Intervention hospitals

At the pre-intervention phase, the proportion of completed field was highest in the following fields- treatment centre (100%), description of ADR (100%) and this remained the same post intervention. An improvement was observed in the all fields regarding drug details. However, fields regarding dates reaction ended, prolongation of hospital stay, treatment of reaction had low levels of completion in most forms. Table 4.

Non- intervention hospitals

There were no remarkable changes in the completion of the field elements except for dates of reports. Table 4.

Table 4: Elements of the National Pharmacovigilance Centre Adverse drug reaction form and proportion of completed fields in the submitted ADR reports in all six hospitals pre and post intervention.

Elements completed (%)	Intervention hospitals			Non-intervention hospitals		
	Pre-intervention n = 57	Post-Intervention n = 75	p value*	Pre-intervention n =10	Post – intervention n = 5	p value*
Hospital number	64.9	72	0.251	100	20	0.009
Age	96.5	97.3	0.780	90	100	1.000
Sex	100	98.7	0.383	100	100	1.000
Weight	42.1	50.7	0.329	0	20	0.714
Treatment centre	100	100	1.000	100	100	1.000
ADR description	100	100	1.000	100	100	1.000
Date reaction started	93.0	92.0	0.833	100	100	1.000
Date reaction ended	47.4	42.7	0.590	90	60	0.171
Admitted due to ADR	98.2	93.3	0.180	70	100	0.171
Prolongation of hospital stay	29.8	38.7	0.291	0*	40	
Treatment of reaction	40.4	42.7	0.789	50	20	0.264
Outcome	71.9	65.3	0.420	50	80	0.264
Brand name	75.4	90.7	0.018	90	100	1.000
Generic name	84.2	96	0.020	90	60	0.494
Batch No	54.4	73.3	0.024	60	40	0.855
NAFDAC No	45.6	69.3	0.006	60	60	1.000
Expiry Date	64.9	85.3	0.006	60	60	1.000
Manufacturers address	54.4	70.7	0.054	50	60	1.000
Indication	93.0	97.3	0.235	90	100	1.000
Dosage	89.5	92.0	0.617	100	100	1.000
Route of administration	77.2	74.7	0.737	80	60	0.836
Date drug started	91.2	92.0	0.874	100	80	0.714
Date stopped	82.5	76	0.369	80	80	1.000
Concomitant medicines	82.5	88.0	0.369	40	100	0.025
Reporter's name	91.2	98.7	0.042	90	100	1.000
Address	93.0	100	0.020	90	100	1.000
Profession	93.0	100	0.020	90	100	1.000
Date	91.2	90.7	0.912	10	80	0.007
Phone number	59.6	82.7	0.003	60	20	0.360
Email address	43.9	36	0.360	40	40	1.000

[1]One of the centres had modified the National Adverse Drug reaction reporting form to exclude prolongation of hospital stay. * chi square

Discussion

This study on ADR reporting is the first in-depth study on the numbers and types of adverse reactions emanating from various teaching hospitals in a zone before and after an intervention. Considering the population and the level of awareness of both the health professionals and the public, the numbers reported does not reflect the burden of adverse drug reactions that exists in a developing country. The numbers of ADR reports shows a slowly growing yet immature pharmacovigilance system. There was a 31% increase in the numbers of ADR reports with intervention. The utilisation of the short messaging system (SMS) to deliver reminders may have accounted for the results obtained as HCP may have paid some attention to messages received. Other studies have found a dual approach to educational intervention useful[38,39]. Frequent lectures or repeated interactive workshops may be an additional approach to stimulating a change in behaviour as suggested by Forsetlund et al[40]. It was noted in this study that the number of reports increased in the immediate post intervention phase which may be ascribed to the effect of the educational lecture and other instructional materials given, as well as the sensitisation and awareness the SMS reinforcements may have added in the short term. However, reports decreased over time as seen in some other studies[19,38] which may be due to the instabilities in the Nigerian health sector and perhaps the healthcare professionals becoming too busy to report despite the SMS reminders.

ADR profile

The mean age of patients with ADR in this study showed that most patients were middle aged which could be ascribed to the population life expectancy in Nigeria although ADRs have been reported to increase with increasing age[41]. We also observed an increase in the number of reports concerning children and adolescents post intervention in this study. It is interesting to note that all the reports in the pre-intervention phase were only antibacterials for systemic use (anti-infectives) but post intervention there were reports to vaccines, antiprotozoals, anti-infectives as well as other drug classes. This may be a small but is a significant gain regarding the scope of products and the reporting culture of those who treat or attend to children and adolescents. The poor reporting rates of ADRs in children were also shown in another study[17]. The sex differences revealed that more females reported more ADRs than males, this may be because females tend to visit the hospitals more and with a different disclosure attribute tending to report most of their complaints, it could also be due to hormonal influences and as seen in earlier studies, gender differences is an important factor in ADR causation[3,42].

The highest proportion of classes of medicines suspected of causing ADRs in this study were anti-infectives for systemic use which on further analysis were mainly antiretroviral medicines and antibacterials. (pre and post intervention), this reflects the burden of communicable diseases in a developing country like Nigeria[43]. Furthermore, HIV medicines are given out freely or heavily subsidized in public health programmes where reporting ADRs is encouraged and expected. A similar pattern was observed in the ADR reports emanating from Africa in a review of ADR reports in Vigibase™[44]. Medicines acting on the renin-angiotensin system were the highest contributors to ADRs attributed to cardiovascular medicines, this group of medicines have been reported to have a higher prevalence of ADRs in blacks[45], and although the numbers are few in this study, it is notable because most of the reactions were serious ADRs. Furthermore, previous studies had demonstrated a high proportion of Nigerian patients developing ADRs to renin-angiotensin system medicines[45,46] despite the prescription pattern of antihypertensives in

the region showing that diuretics and calcium channel blockers were the most prescribed [46]. This differential presentation may require further evaluation. It is noteworthy that tramadol was the single most implicated medicine causing ADRs as it is a commonly used analgesic in Nigeria [48,49]. However, the number of tramadol ADR reports from Africa is about 1% in the Vigibase™ via Vigiaccess™ indicating that the adverse effects profile of tramadol and prevalence of abuse is underestimated despite some reports of misuse and abuse and a NAFDAC alert[50,51]. The safety profile of tramadol in blacks needs proper analysis in view of the findings above.

The involvement of skin and subcutaneous tissue disorders as the most prominent system in ADRs could be ascribed to the easily observed and cosmetic nature of dermatological disorders. This may make identification of the ADR easier by both patient and HCP. Also, the immunologic and metabolic activity of the skin makes it susceptible to ADRs[51]. This pattern of presentation of the skin and subcutaneous tissue ADRs is also similar to the rest of Africa [43]. Other implicated systems include the nervous system, as well as the gastrointestinal system.

The number of fatal cases reported in the post intervention period may also be a pointer to the depth of disclosure and willingness of reporters in reporting suspected medicine related incidents as no case was reported in the pre intervention period. In a developing pharmacovigilance system reporting all suspected ADR cases is encouraged. Although the medicines could not be identified in 2 of the cases, the reports could be due to possible behavioural change from the intervention. The use of multiple medications is also a reflection of the pattern of irrational use of medicines in our setting[10].

Reporters

In this study, all cadres of healthcare professionals reported an ADR in the pre-intervention phase, notably in one institution nurses had reported ADRs which may be due to previous training on ADR reporting at that centre. Another study had shown that nurses mainly report using their ward report book or verbal report to the doctor[12]. There may be a need to undertake targeted training in all stages of professional development in order to encourage nurses to inculcate an ADR reporting culture using the ADR reporting form. The study also revealed that more pharmacists reported after the intervention as they may have felt it was an obligation to report ADRs[52,53]. This may not be the case with nurses, it is therefore imperative to devise methods that can improve the practice of reporting. The physicians in this study submitted more valid reports and this could account for the observation in the study by Bergvall et al that showed that more doctors in Nigeria submitted more complete reports to the Vigibase™ than other health care workers.[54] This could be a reflection of the activities of the National Pharmacovigilance Centre awareness campaigns in Nigeria and could be a function of the baseline knowledge of the physicians. However, the attitudes and barriers to reporting as shown by other studies[12,52] will have to be surmounted to improve reporting by all healthcare professionals.

Completeness

The intervention targeted both an increase in the numbers of reports as well as quality of reports. Quality in pharmacovigilance has many facets[55] and an important part is determination of the validity of the report to ascertain if it meets the minimum requirements for reporting according to the ICH guidelines[33]. The proportion of valid cases

in the study was high and increased with intervention. This may be a reflection of the intervention which may have also helped to further underscore the need to fill as many fields as possible to enable for appropriate signal detection.

One of the aims of reporting ADRs is to detect signals and ensure that medicines that have greater risks than benefits are either withdrawn or restricted. Causality or imputation methods using data from the ADR reports are useful in achieving this aim[35], therefore, the completeness of data in the forms is essential. Evaluating the fields in the Nigerian National ADR reporting form in this study showed that key fields such as date reaction stopped, date drug was stopped as well as outcome were important elements missing from some reports even after the intervention, this may be due to inattention to the importance of dates in the determination of an ADR by the HCPs when the seminar was given. This may affect the usability of these reports in the Vigibase and accounted for some of the forms that were unassessable after causality assessment was undertaken. The reasons for these incompletely filled fields may be related to the inability of healthcare professional to follow up ADR cases due to logistic issues and lack of adequate funding of the pharmacovigilance set up[10]. Other studies have equally shown that missing information is prevalent worldwide[56,57]. It is therefore imperative to further emphasise these issues in future interventions. Furthermore, due to drug quality issues in Nigeria, the regulatory agency number as well as expiry date evaluated in the forms also had missing information. This information is useful in our setting as the prevalence of use of substandard falsified medical products is high [58]and this may be an approach towards ascertaining if the suspected medicinal product is approved for use in Nigeria. These are key fields that ought to accompany as many reports as possible.

Although the NPC form has undergone some revisions since it was first developed, there may be a need to evaluate ways to improve the reporting culture of healthcare professionals using the form.

Limitations

Some limitations were encountered in this study, firstly some of the institutions already had some pharmacovigilance mechanism in place that could have accounted for the results seen but this appeared not to have made any difference in the results post intervention. Also during the periods of the study, the Nigerian health sector underwent industrial disruptions at varying times resulting in reduced number of patients visiting the hospitals and as such this may have contributed to the few numbers of ADR reports seen but the situation was equally same in the pre-intervention phase, therefore we are of the opinion that only interested health care professionals would report regardless of the patient load. There was a clear absence of reporting culture which accounted for the low reporting rates and the inability of the healthcare professionals to recognize adverse events appears to have limited the few events reported to skin related ADRs and those that are serious. The non-intervention hospitals had very few reports during the study and the sizes of the hospitals could have accounted for this observation, thus we did not compare the intervention hospitals with the non intervention hospitals. Furthermore, a randomisation which was carried out at the onset of the study was to avoid a bias in selecting the hospitals. A concerted effort was made to eliminate contamination of the population but this could not be fully ruled out.

Conclusions

In conclusion, there appeared to be a gain following the intervention in the absolute numbers, the increment in the number of valid reports and in the completeness in the fields of the ADR form. There is urgent need for educational strategies to further sensitise and train the HCP and raise the awareness of the health-related and general population regarding pharmacovigilance. Development of other interventional strategies to increase the number of reports is also essential and there may be a need to target nurses at the formative stages of their training in view of their extremely low participation despite the education received. A review of the training curriculum of HCP is required to address the identified knowledge, attitudinal and practice gap. Furthermore, development of additional reporting modes and possibly a revision of the NPC reporting form are needed to improve the data being sent to the WHO Programme for International Drug Monitoring (PIDM). Further research to evaluate the effects of specific medicines such as those acting on the renin-angiotensin system and other opioids in the Black population is of importance.

Funding: This study was self funded

Conflicts of Interest: the Authors declare no conflicts of interest regarding this work.

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Supplemental Information 1: Monthly text messages sent to the health care professionals in the intervention arm of the South- South Zone of Nigeria over 12 months.

1. Drug Rxn SSZPC
Pharmacovigilance
Please report all adverse drug reaction cases using YELLOW FORMS to the Drug Information Center in OPD pharmacy.
Or call Pharm in charge on 08027640022.
Or scan & email the report to zpcsouthsouth@gmail.com. 09092474258

2. Drug Rxn SSZPC
Pharmacovigilance
Please report all adverse drug reaction cases using YELLOW FORMS to the Drug Information Center in OPD pharmacy.
Or call Pharm in charge on 08027640022.
Or scan & email the report to zpcsouthsouth@gmail.com. 09092474258

3. Drug RXN
Pharmacovigilance: Report ALL ADVERSE DRUG REACTIONS with NAFDAC FORMS to DPIC/COPD pharmacy, or call 08033733534, 08037075435 or email ZPC at zpcsouthsouth@gmail.com

4. Drug RXN
Adverse drug reactions are NOXIOUS unintended response to drugs used at normal doses. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

5. Drug RXN
Adverse drug reactions are NOXIOUS unintended response to drugs used at normal doses. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

6. Drug RXN
Adverse drug reactions can be known or new, could be delayed for a long time or occur at the end of use. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022
Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

7. Drug Rxn
There are no penalties for reporting an adverse drug reaction. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022.Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

8. Drug Rxn
Reporting Drug reactions aids patient safety. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022.Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

9. Drug Rxn
Season greetings, ALL adverse drug reactions should be reported. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022

10. Drug Rxn

Season greetings, ALL adverse drug reactions should be reported. Please report any suspected case to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022. Or email it to zpcsouthsouth@gmail.com. or call 08037075435.

11. Drug Rxn

It takes 10 minutes to report DRUG REACTIONS. ALL suspected cases should be reported to the pharmacovigilance centre in the hospital using the NAFDAC Yellow Form. Or call 08027640022 08037075435. Or email it to zpcsouthsouth@gmail.com

12. Drug Rxn

Call the Pharmacovigilance Unit on 08027640022 or 08037075435 to report ALL suspected adverse drug reactions in the hospital OR use the NAFDAC Yellow Form. Or email it to zpcsouthsouth@gmail.com

Impact of an educational intervention on adverse drug reaction reporting in tertiary hospitals in South-South Nigeria.
Abimbola O. Opadeyi, Annie Fourrier-Réglat, Ambrose O. Isah,
Supplemental Information II: Anatomical Chemical Classification (ATC) of suspected medicines and MedDRA Preferred Term (PT) of associated ADRs for selected drug classes.

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
Anti-infectives For Systemic Use(63)	Antivirals For Systemic Use(39)	Zidovudine, Lamivudine and Nevirapine	J05AR05	17	10038205	Ocular Hyperaemia	Eye Disorders	1
					10029845	Paraesthesias And Dysaesthesias	Nervous System Disorders	1
					10019211	Headache	Nervous System Disorders	3
					10042722	Joint Swelling	Musculoskeletal And Connective Tissue Disorder	1
					10046665	Oliguria	Renal And Urinary Disorders	1
					10012794	Gait Disturbance	General Disorders And Administration Site Conditions	1
					10033557	Palpitations	Cardiac Disorders	1
					10013573	Dizziness	Nervous System Disorders	1
					10005886	Vision Blurred	Eye Disorders	1
					10022437	Insomnia	Psychiatric Disorders	3
					10061145	Eyelid Function Disorder	Eye Disorders	1
					10047700	Vomiting	Gastrointestinal Disorders	2
					10012735	Diarrhoea	Gastrointestinal Disorders	1
					10006345	Dyspnoea	Respiratory, Thoracic And Mediastinal Disorders	2
					10047862	Asthenia	General Disorders And Administration Site Conditions	2
					10014232	Oedema Generalised	General Disorders And Administration Site Conditions	2

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions PT)
					10062821	Oral Dysaesthesia	Gastrointestinal Disorders	1
					10028813	Nausea	Gastrointestinal Disorders	1
Anti-infectives For Systemic Use(63)	Antivirals For Systemic Use(39)				10041466	Speech Disorder	Nervous System Disorders	1
					10000081	Abdominal Pain	Gastrointestinal Disorders	1
					10049365	Lip Exfoliation	Gastrointestinal Disorders	1
					10039999	Feeling Hot	General Disorders And Administration Site Conditions	1
					10037889	Exfoliative Rash	Skin And Subcutaneous Tissue Disorders	1
					10001768	Alopecia	Skin And Subcutaneous Tissue Disorders	1
					10016335	Feeling Of Body Temperature Change	General Disorders And Administration Site Conditions	1
					10054849	Face Oedema	General Disorders And Administration Site Conditions	1
					10047386	Vestibular Disorder	Ear And Labyrinth Disorders	1
					10034206	Oedema Peripheral	General Disorders And Administration Site Conditions	1
					10040908	Skin Exfoliation	General Disorders And Administration Site Conditions	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions PT)
Anti-infectives For Systemic Use(63)	Antivirals For Systemic Use(39)	Lamivudine, Tenofovir disoproxil And Efavirenz	J05AR11	9	10010300	Confusional State	Psychiatric Disorders	1
					10052407	Paraesthesia	Nervous System Disorders	1
					10047700	Vomiting	Gastrointestinal Disorders	1
					10028813	Nausea	Gastrointestinal Disorders	2
					1004660	Pollakiuria	Renal And Urinary Disorders	1
					10029845	Hypoaesthesia	Nervous System Disorders	2
					10047862	Asthenia	General Disorders And Administration Site Conditions	1
					10013573	Dizziness	Nervous System Disorders	2
					10019063	Hallucination	Psychiatric Disorders	2
					10033799	Paralysis	Nervous System Disorders	1
					10022437	Insomnia	Psychiatric Disorders	
					10029412	Nightmare	Psychiatric Disorders	2
					10012791	Dyspnoea	Respiratory, Thoracic And Mediastinal Disorders	1
					10021630	Incoherent	Nervous System Disorders	1
		Lamivudine and Abacavir	J05AR02	4	10034716	Vomiting	Gastrointestinal Disorders	1
					10047864	Asthenia	General Disorders And Administration Site Conditions	1
					10048324	Dizziness	Nervous System Disorders	1
					10048358	Abdominal Pain	Gastrointestinal Disorders	1
					10022437	Insomnia	Psychiatric Disorders	1
					10003028	Decreased Appetitie	Metabolism And Nutrition Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
		Abacavir	J05AF06	2	10037844	Rash	Skin And Subcutaneous Tissue Disorders	2
					10063543	Myalgia	Musculoskeletal And Connective Tissue Disorders	1
					10023084	Pruritus	Skin And Subcutaneous Tissue Disorders	1
		Efavirenz	J05AG03	2	10033775	Paraesthesia	Nervous System Disorders	1
					10048567	Headache	Nervous System Disorders	1
					10038743	Restlessness	Psychiatric Disorders	1
					10022989	Thinking Abnormal	Psychiatric Disorders	1
					10004206	Abnormal Behaviour	Psychiatric Disorders	1
		Nevirapine	J05AG01	1	10049365	Lips Exfoliation	Gastrointestinal Disorders	1
					10033726	Rash Papular	Skin And Subcutaneous Tissue Disorders	1
					10077181	Rash Maculo-Papular	Skin And Subcutaneous Tissue Disorders	1
		Zidovudine and Lamivudine	J05AR01	2	10019211	Headache	Nervous System Disorders	1
					10049800	Hypoaesthesia	Nervous System Disorders	1
		Zidovudine, Lamivudine and Abacavir	J05AR04	1	10078943	Headache	Nervous System Disorders	1
		Lopinavir, Ritonavir	J05AR10	1	10072268	Drug-Induced Liver Injury	Hepatobiliary Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
	Antibacterials for systemic use(19)	Amoxicillin And Enzyme Inhibitor	J01CR02	6	10018095	Rash Generalised	Skin And Subcutaneous Tissue Disorders	1
					10047884	Asthenia	General Disorders And Administration Site Conditions	1
					10005886	Vision Blurred	Eye Disorders	1
					10034186	Haematocrit Decreased	Investigations	1
					10047377	Rash Vesicular	Skin And Subcutaneous Tissue Disorders	1
					10019211	Headache	Nervous System Disorders	1
					10039177	Chills	General Disorders And Administration Site Conditions	1
					10048971	General Body Pain	General Disorders And Administration Site Conditions	1
					10012735	Diarrhoea	Gastrointestinal Disorders	1
					10028813	Nausea	Gastrointestinal Disorders	1
					10063438	Pruritus Allergic	Skin And Subcutaneous Tissue Disorders	1
					10047700	Vomiting	Gastrointestinal Disorders	1
					10018103	Urticaria	Skin And Subcutaneous Tissue Disorders	1
					10016015	Lacrimation Increased	Eye Disorders	1
					10016009	Ocular Hyperaemia	Eye Disorders	1
					10011232	Cough	Respiratory, Thoracic And Mediastinal Disorders	1
					10056647	Eye Swelling	Eye Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	Meddra Code	PT	SOC	Number of reactions (PT)
					10018771	Nasal Congestion	Respiratory, Thoracic And Mediastinal Disorders	1
					10013963	Dyspnoea	Respiratory, Thoracic And Mediastinal Disorders	1
		Sulfamethoxazole and Trimethoprim	J01EE01	3	10049201	Generalized Rash	Skin And Subcutaneous Tissue Disorders	2
					10044223	Toxic Epidermal Necrolysis	Skin And Subcutaneous Tissue Disorders	1
		Metronidazole	J01XD01	1	10043071	Tachycardia	Cardiac Disorders	1
					10018066	Malaise	General Disorders And Administration Site Conditions	1
		Ciprofloxacin	J01MA02	2	10049201	Generalized Rash	Skin And Subcutaneous Tissue Disorders	1
					10018103	Urticaria	Skin And Subcutaneous Tissue Disorders	1
		Moxifloxacin	J01MA14	1	10040015	Deafness Neurosensory	Ear And Labyrinth Disorders	1
					10043882	Tinnitus	Ear And Labyrinth Disorders	1
		Levofloxacin	J01MA12	1	10047864	Asthenia	General Disorders And Administration Site Conditions	1
					10049201	Generalized Rash	Skin And Subcutaneous Tissue Disorders	1
		Chloramphenicol	J01BA01	1	10033730	Rash Papular	Skin And Subcutaneous Tissue Disorders	1
					10037853	Exfoliative Rash	Skin And Subcutaneous Tissue Disorders	1
		Amoxicillin	J01CA04	1	10078737	Rash Vesicular	Skin And Subcutaneous Tissue Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term(PT)	System Organ Classification	Number of reactions (PT)
					10038205	Ocular Hyperaemia	Eye Disorders	1
					1049365	Lips Exfoliation	Gastrointestinal Disorders	1
					10071911 9	Vulva Haemorrhage	Reproductive System And Breast Disorders	1
		Combination Of Penicillins	J01CR50	1	10018095	Rash Generalised	Skin And Subcutaneous Tissue Disorders	1
					10056647	Eye Swelling	Eye Disorders	1
		Cefotaxime	J01DD01	1	10025424	Rash Maculo-Papular	Skin And Subcutaneous Tissue Disorders	1
		Ceftriaxone	J01DD04	1	10018103	Urticaria	Skin And Subcutaneous Tissue Disorders	1
					10020202	Dysphonia	Respiratory, Thoracic And Mediastinal Disorders	1
					10037087	Pruritus	Skin And Subcutaneous Tissue Disorders	1
	Antimycobacterials(2)	Isoniazid	J04AC01	2	10008492	Chest Discomfort	General Disorders And Administration Site Conditions	1
					10012791	Dyspnoea	Respiratory, Thoracic And Mediastinal Disorders	1
					10015967	Eye Swelling	Eye Disorders	1
	Antimycotics for systemic use(1)	Fluconazole	J02AC01	1	10023084	Pruritus	Skin And Subcutaneous Tissue Disorders	1
					10015244	Rash Erythematous	Skin And Subcutaneous Tissue Disorders	1
					10073477	Rash Erythematous	Skin And Subcutaneous Tissue Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
	Vaccines(2)	Pnuemococcus, Purified Polysaccharides Antigen Conjugated	J07AL02	1	10005928	Furuncle	Infections And Infestations	1
					10078737	Blistery Rash	Skin And Subcutaneous Tissue Disorders	1
		Measles, Live Attenuated	J07BD01	1	10077181	Rash Maculo-Papular	Skin And Subcutaneous Tissue Disorders	1
					10016558	Pyrexia	General Disorders And Administration Site Conditions	1
					10003028	Decreased Appetite	Metabolism And Nutrition Disorders	1
Antiparasitic Products, Insecticides And Repellents(17)	Antiprotozoals (17)	Artesunate And Mefloquine	P01BF02	5	10006772	Thermal Burn	Injury, Poisoning And Procedural Complications	1
					10046735	Urticaria	Skin And Subcutaneous Tissue Disorders	1
					10044565	Tremor	Nervous System Disorders	1
					10013649	Somnolence	Nervous System Disorders	1
					10027600	Migraine	Nervous System Disorders	1
					10016256	Fatigue	General Disorders And Administration Site Conditions	1
					10048415	Fatigue	General Disorders And Administration Site Conditions	1
					10033556	Palpitations	Cardiac Disorders	1
					10066202	Presyncope	Nervous System Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
					10010300	Confusional State	Psychiatric Disorders	1
					10027600	Migraine	Nervous System Disorders	1
					10015243	Rash Erythematous	Skin And Subcutaneous Tissue Disorders	1
					10018201	Tongue Geographic	Gastrointestinal Disorders	1
					10019458	Haematuria	Renal And Urinary Disorders	1
					10064579	Exfoliative Rash	Skin And Subcutaneous Tissue Disorders	1
					10056671	Mucocutaneous Rash	Skin And Subcutaneous Tissue Disorders	1
		Artemether And Lumefantrine	P01BF01	4	10023092	Itchy Rash	Skin And Subcutaneous Tissue Disorders	1
					10040841	Rash	Skin And Subcutaneous Tissue Disorders	1
					10042703	Lip Swelling	Gastrointestinal Disorders	1
					10042706	Swollen Tongue	Gastrointestinal Disorders	1
					10005260	Burns Second Degree	Injury, Poisoning And Procedural Complications	1
					10025418	Rash Macular	Skin And Subcutaneous Tissue Disorders	1
					10037576	Rash Pustular	Infections And Infestations	1
		Artenimol And Piperaquine	P01BF05	4	10037844	Rash	Skin And Subcutaneous Tissue Disorders	1
					10066202	Presyncope	Nervous System Disorders	1
					10013573	Dizziness	Nervous System Disorders	1
					10016558	Pyrexia	General Disorders And Administration Site Conditions	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
					10016256	Fatigue	General Disorders And Administration Site Conditions	1
					10019256	Hypoacusis	Ear And Labyrinth Disorders	1
					10039897	Sedation	Nervous System Disorders	1
					10078737	Rash Vesicular	Skin And Subcutaneous Tissue Disorders	1
					10023084	Pruritus	Skin And Subcutaneous Tissue Disorders	1
					10016008	Asthenopia	Eye Disorders	1
		Artesunate-Amodiaquine	P01BF03	2	10047862	Asthenia	General Disorders And Administration Site Conditions	1
					10028813	Nausea	Gastrointestinal Disorders	1
					10003028	Decreased Appetite	Metabolism And Nutrition Disorders	1
					10024264	Lethargy	Nervous System Disorders	1
					10022437	Insomnia	Psychiatric Disorders	1
					10013986	Dystonia	Nervous System Disorders	1
		Arthemether (IM)	P01BE02	1	10033556	Palpitations	Cardiac Disorders	1
		Quinine	P01BC01	1	10020466	Hunger	General Disorders And Administration Site Conditions	1
					10013573	Dizziness	Nervous System Disorders	1
					10024855	Loss Of Consciousness	Nervous System Disorders	1
Cardiovascular System(14)	Agents acting on the renin Angiotensin System(12)	Lisinopril	C09AA03	4	10042723	Lip Swelling	Gastrointestinal Disorders	2
					10019211	Headache	Nervous System Disorders	1
					10049351	Cheilitis	Gastrointestinal Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
					10066202	Presyncope	Nervous System Disorders	1
					10043071	Tachycardia	Cardiac Disorders	1
					10079443	Angioedema	Skin And Subcutaneous Tissue Disorders	2
		Ramipril	C09AA05	4	10018085	Pruritus Generalised	Skin And Subcutaneous Tissue Disorders	1
					10053262	Skin Swelling	Skin And Subcutaneous Tissue Disorders	1
					10042690	Eyelid Oedema	Eye Disorders	1
					10042684	Lip Swelling	Gastrointestinal Disorders	1
					10016558	Pyrexia	General Disorders And Administration Site Conditions	1
					10040842	Erythema	Skin And Subcutaneous Tissue Disorders	1
					10021005	Hypoglycaemia	Metabolism And Nutrition Disorders	1
					10012752	Blood Pressure Diastolic Decreased	Investigations	1
					10042706	Swollen Tongue	Gastrointestinal Disorders	1
					10039381	Salivary Hypersecretion	Gastrointestinal Disorders	1
					10028296	Muscle Spasms	Musculoskeletal And Connective Tissue Disorders	1
		Valsartan	C09CA03	2	10047864	Asthenia	General Disorders And Administration Site Conditions	1
					10024264	Lethargy	Nervous System Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
					10064927	Therapy Change	Surgical And Medical Procedures	1
					10033557	Palpitations	Cardiac Disorders	1
		Lorsatan Potassium	C09CA01	1	10012735	Diarrhoea	Gastrointestinal Disorders	1
					10013773	Cough	Respiratory, Thoracic And Mediastinal Disorders	1
		Perindopril And Amlodipine	C09BB04	1	10078746	Hemiparaesthesia	Nervous System Disorders	1
	Calcium Channel Blockers(1)	Nifedipine	C08CA05	1	10071065	Pollakiuria	Renal And Urinary Disorders	1
Musculoskeletal System(10)	Antiinflammatory And Antirheumatic Products(	Diclofenac	M01AB05	3	10068748	Rash	Skin And Subcutaneous Tissue Disorders	1
					10078737	Rash Vesicular	Skin And Subcutaneous Tissue Disorders	2
					10042700	Peripheral Swelling	General Disorders And Administration Site Conditions	1
					10071910	Upper Gastrointestinal Haemorrhage	Gastrointestinal Disorders	1
					10056647	Eye Swelling	Eye Disorders	1
					10011224	Cough	Respiratory, Thoracic And Mediastinal Disorders	1
					10010723	Conjunctival Hyperaemia	Eye Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
		Aceclofenac	M01AB16	1	10071910	Upper Gastrointestinal Haemorrhage	Gastrointestinal Disorders	1
		Ibuprofen	M01AE01	1	10042030	Stevens-Johnson Syndrome	Skin And Subcutaneous Tissue Disorders	1
		Piroxicam	M01AC01	1	10071910	Upper Gastrointestinal Haemorrhage	Gastrointestinal Disorders	1
		Multiple NSAIDS		1	10027141	Melaena	Gastrointestinal Disorders	1
					10019418	Haematemesis	Gastrointestinal Disorders	1
		Glucosamine	M01AX05	1	10013573	Dizziness	Nervous System Disorders	1
Nervous System(13)	Analgesics(4)	Tramadol	N02AX02	2	10023092	Rash Pruritic	Skin And Subcutaneous Tissue Disorders	1
					10008492	Chest Discomfort	General Disorders And Administration Site Conditions	1
					10050819	Musculoskeletal Chest Pain	Musculoskeletal And Connective Tissue Disorders	1
					10047862	Asthenia	General Disorders And Administration Site Conditions	1
					10016065	Swelling Face	Skin And Subcutaneous Tissue Disorders	1
					10042706	Swelling Of Tongue	Gastrointestinal Disorders	1
					10023556	Dyspnoea	Respiratory, Thoracic And Mediastinal Disorders	1

Level 1 ATC	Level 2 ATC	Drug Name	ATC	No of patients	MedDRA Code	Preferred Term	System Organ Classification	Number of reactions (PT)
		Paracetamol, Combinations Excl. Psycholeptics	N02BE51	1	10013573	Dizziness	Nervous System Disorders	1
					10042771	Syncope	Nervous System Disorders	1
		Pentazocine	N02AD01	1	10008589	Choking	Respiratory, Thoracic And Mediastinal Disorders	1

.CHAPTER 7:

A PROFILE OF ADVERSE EFFECTS OF ANTIHYPERTENSIVE MEDICINES IN A TERTIARY CARE CLINIC IN NIGERIA

Chapter 7 A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria

Olowofela A, Isah AO. A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria. Annals of African Medicine 2017; 16: 114–119.

Final publication available at: http://www.annalsafrmed.org/article.asp?issn=1596-3519;year=2017;volume=16;issue=3;spage=114;epage=119;aulast=Olowofela

Original Article

A Profile of Adverse Effects of Antihypertensive Medicines in a Tertiary Care Clinic in Nigeria

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Abstract

Background: There has been a dearth of comprehensive data on the profile of adverse reactions to antihypertensive medicines in the Nigerian setting despite increased use. **Objective:** This study was aimed to characterize the adverse reactions experienced in the homogenously black African population. **Methods:** The study was carried out at the University of Benin Teaching Hospital, Benin City, Nigeria, in consenting eligible hypertensive patients ≥18 years. Adverse reactions were sought using patient's self-report and a medicine-induced symptom checklist. **Results:** A total of 514 patients (340 females) aged 22–97 years were studied. Thirteen percent, 27.6%, 26.7%, 22.0%, and 10.7% were on 1, 2, 3, 4, and ≥5 medicines, respectively, for control of their blood pressure with the frequency of adverse effects increasing proportionately up to four medicines. Adverse reactions to antihypertensive medicines were reported by a total of 93 (18.1%) patients. Diuretics – 27.9%, calcium channel blockers (CCBs) – 26.8%, and angiotensin-converting enzyme inhibitors (ACEIs) – 26.8% accounted for most of the adverse reactions seen, notably frequent micturition and headaches (CCB); excessive micturition and dizziness (diuretics); dry irritating cough (ACEI). Notable complaints for all patients using the checklist were increased frequency of micturition, reduction in libido, and headaches. The reactions resulted in the discontinuation and substitution of therapy in 49.5% of the patients. **Conclusions:** The characterization of these reactions in Nigerians requires further studies as frequent micturition reported is still a neglected complaint in antihypertensive therapy.

Keywords: Adverse drug reactions, antihypertensive agents, Nigeria

Résumé

Contexte: Il y a eu une pénurie de données complètes sur le profil des réactions indésirables aux médicaments antihypertenseurs dans le cadre nigérian malgré une utilisation accrue. **Objectif:** Cette étude visait à caractériser les effets indésirables de la population africaine homogène noir. **Méthodes:** L'étude a été réalisée à l'hôpital universitaire de l'Université du Bénin, dans la ville de Benin, au Nigeria, dans des patients hypertendus admissibles ≥18 ans qui ont consenti à l'étude. Des réactions indésirables ont été recherchées en utilisant l'auto-évaluation du patient et une liste de contrôle des symptômes induite par un médicament. **Résultats:** Un total de 514 patients (340 femmes) âgés de 22 à 97 ans ont été étudiés. Treize pour cent, 27,6%, 26,7%, 22,0% et 10,7% étaient en 1, 2, 3, 4 et ≥5 médicaments, respectivement, pour le contrôle de leur pression artérielle avec la fréquence des effets indésirables augmentant proportionnellement jusqu'à quatre médicaments. Les réactions indésirables aux antihypertenseurs ont été rapportées par un total de 93 patients (18,1%). Les diurétiques - 27,9%, les inhibiteurs des canaux calciques (CCB) - 26,8% et les inhibiteurs de l'enzyme de conversion de l'angiotensine (ACEI) - 26,8% ont représenté la plupart des effets indésirables observés, notamment la miction et les maux de tête fréquents (CCB); Miction excessive et vertiges (diurétiques); Toux irritante sèche (ACEI). Des plaintes notables pour tous les patients utilisant la liste de contrôle étaient une fréquence accrue de miction, une réduction de la libido et des maux de tête. Les réactions ont entraîné l'arrêt et la substitution du traitement chez 49,5% des patients. **Conclusions:** La caractérisation de ces réactions chez les Nigérians nécessite d'autres études car les miction fréquentes rapportées sont encore une plainte négligée dans le traitement antihypertenseur.

Mots-clés: Effets indésirables des médicaments, agents antihypertenseurs, Nigéria

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Access this article online

Quick Response Code:

Website: www.annalsafrmed.org

DOI: 10.4103/aam.aam_6_17

How to cite this article: Olowofela AO, Isah AO. A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria. Ann Afr Med 2017;16:114-9.

Introduction

Hypertension is a global disease considered as the leading risk factor for cardiovascular diseases with significant health burden and accounts for 9.4 million deaths as well as 7.0% disability-adjusted life years (DALYs) of global DALYs in 2010.[1] The prevalence in Nigeria is estimated at over 28.9%.[2] It is associated with a high morbidity and mortality, from increased risks of stroke, ischemic heart disease, renal failure, congestive heart failure as well hypertensive heart diseases and the observation that it is worse in people of black ancestry.[1,3-5] The use of medicines and other forms of nonpharmacological therapy in treating hypertension has been shown to reduce this morbidity and mortality.[6,7] There has been a considerable increase in the arsenal of antihypertensive medicines in the past few decades, and their use may be associated with the development of adverse reactions which is likely to result in nonadherence to therapy, increased morbidity and mortality as well as economic consequences.[8,9] It has also led to the withdrawal of some of these medicines from use.[10]

Adverse reactions in outpatient care have been estimated to occur in about 25% of patients[11] and factors that have been associated with increased frequency of adverse reactions include, number of medicines taken by the patient's genetic disposition, age, pregnancy, and exogenous factors such as food and interactions with other medicines.[12] Identification of adverse reactions using different methods has also been advocated to limit the poor prognosis that is associated with adverse reactions.[11] The profile of adverse reactions to antihypertensive medicines in our environment has not been properly characterized given the antihypertensive armamentarium in use in this setting. There is a need to properly characterize the tolerability profile of these medicines in this environment.

Methods

This cross-sectional study was carried out at the consultant medical outpatient department (COPD) of a tertiary hospital in Southern Nigeria. The teaching hospital is a 730-bed tertiary center, which also serves as a referral center to the neighboring states of Ondo, Anambra, Bayelsa, and Delta states. The COPD houses the hypertension clinic as well as other medical subspecialties. The study was carried out over 9 months and patients with a diagnosis of hypertension on therapy who attended the medical outpatient clinic. Hypertensive patients on antihypertensive medicines who were aged 18 years and above and consented to the study were included in the study.

For this cross-sectional study, the sample size calculation was based on a previous study by Isah *et al*.[13] on the assessment of patient's knowledge and experience of hypertension and it revealed that about 24.8% reported that an adverse event affected their compliance. Using this figure as an estimate of the desired proportion of an adverse drug reaction (ADR), at a confidence interval of 95%, the formula for simple proportions was used.[14] A sample of 289 hypertensive patients was the minimum sample size calculated for this study. Furthermore, anticipating a 70% response to the questionnaire a sample size of 376 was estimated. However, 514 patients consented and were recruited into the study.

The patients were classified as being hypertensive (defined according to the Nigerian Hypertension Society guidelines that were based on the 1999 WHO/International Society of Hypertension recommendations), as blood pressure ≥140/90 mmHg.[15] All patients who fulfilled the inclusion criteria and consented to the study were included. During the visit, their demographic characteristics, duration of hypertension as well as comorbidities were recorded in an interviewer-administered questionnaire. Antihypertensive medicines, other prescribed medications and indication for their use were noted, use of other nonprescribed medicines and herbal medicines were also recorded. ADRs to antihypertensive medicines prescribed at the last clinic visit were sought.

Following the self-reported sessions, a modified checklist of antihypertensive medicines – induced symptoms as described by Bulpitt and Dollery[16] and modified based on previous studies[13,17] was administered to the patients to determine what symptoms they experienced that was related to medicine use. Reported adverse reactions were also documented and classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classification,[18] and the probability of the event being an ADR was assessed with the WHO and Naranjo causality algorithms.[19,20] The outcome of the reaction was noted as well as the action patient took following the ADR.

Ethical considerations

Ethical approval was obtained from the Ethics and Research Committee of the University of Benin Teaching Hospital, and informed consent was obtained from each patient verbally. The quality of the data and its confidentiality were ensured by keeping the patients' identity coded with their initials only. The data were fully anonymized and aggregated. Any information about any patient was kept strictly confidential and not shared with unauthorized individuals. The patient's right to confidentiality, information and privacy were respected.

Statistical analysis

Antihypertensive medications were classified into different classes: (angiotensin converting enzyme inhibitors [ACEI], beta-blockers, calcium channel blockers [CCBs], diuretics, centrally acting agents, and angiotensin receptor blockers [ARBs]). Data were analyzed using SPSS (Statistical package for the Social Sciences, SPSS Inc., Chicago, IL, USA) software version 16 for windows. Descriptive and inferential analyses were conducted as appropriate, and level of significance was set at $P < 0.005$.

Results

A total of 514 patients were recruited into the cross-sectional descriptive study. The male:female ratio was 1:2, and the

age ranged from 22 to 97 years with a mean ± (standard deviation [SD]) age of 57.91 ± 12.0 years, there was no statistically significant difference between the mean ages of the men 58.8 (12.4) and women 57.5 (11.8) studied (*t*-test = 0.213; *P* = 0.552). A total of 146 patients (28.4%) were aged 65 years and above. Regarding the educational status of the population, 172 (33.5%) had tertiary education representing the largest group.

The mean (SD) duration of diagnosis of hypertension in the 514 patients was 7.8 (7.9) years, (range: 1 month–40 years) while they had been receiving treatment for a mean (SD) duration of 7.4 (7.8) years (range: 2 weeks–36 years).

Only 16 (3.1%) patients were currently smoking and 67 (13%) admitted to social use of alcohol. Fifty percent (254) of the patients had comorbidities, with 85% having one comorbidity only and 14.2%, 0.8% having two and three, respectively. The different comorbidities as documented in the case records were mainly diabetes mellitus 131 (25.5%), osteoarthritis 78 (15.2%), obesity 16 (3.1%), and peptic ulcer disease 15 (2.9%) among others.

Antihypertensive medicines prescribed

A total of 67 (13%) patients were on one antihypertensive medicine (monotherapy), of which 11/67 (16.4%) of them had only antihypertensive medicine prescribed, whereas the other 56/67 (83.6%) had other medicines besides antihypertensive medicines. Four hundred and forty-seven (87%) were on combination therapy of two or more antihypertensive medicines, (combination therapy). In the patients on combination therapy, 142 (27.63%), 137 (26.63%), 113 (21.98%), and 55 (10.70%) of them had 2, 3, 4, and 5 or more antihypertensive medicines prescribed.

CCBs were the most prescribed class of antihypertensive medicines 362 (70.4%) and alpha-blockers the least prescribed group 9 (1.8%). Beta-blockers 118 (23.0%) and alpha-blockers - 9 (1.8%) were prescribed only in combination therapy. The most common combinations of antihypertensive medicines were diuretics and CCBs. In patients using only one antihypertensive medicine, more patients were on ACEI 31 (46.3%), and this was closely followed by CCB at 26 (38.8%), other medicines used include ARB 5 (7.5%), centrally acting medicine 3 (4.5%), and diuretics 2 (3.0%).

Adverse drug reactions experienced

Ninety-three (18.1%) patients experienced an ADR to their antihypertensive medicines. Using the causality assessment scales to classify the probability of the adverse reactions, with WHO assessment[19] 29 (31.2%), had their adverse reactions classified as probable and 56 (60.2%) as possible. However, 7 (7.5%) and 1 (1.1%) patient(s) had experienced adverse reactions judged as being unlikely and conditional, respectively.

Using the Naranjo assessment algorithm[20] to assess the adverse reactions, 55 (59.1%) were classified as having had a possible adverse reaction, 37 (39.8%) were probable, and 1 (1.1%) was doubtful.

ADRs increased with increase in the number of antihypertensive medicines, and it was statistically significant [Table 1].

Proportionately, more men 35/174 (20.1%) than women 58/340 (17.1%) reported an adverse reactions to their antihypertensive medications, but it was not statistically significant ($\chi^2 = 0.725$, df = 1, $P = 0.39$). Elderly patients 20/146 (13.7%) reported fewer ADR compared to younger patients 73/368 (19.8%), although it was not significant. ($\chi^2 = 2.658$. df = 1. $P = 0.103$).

Profile of adverse reactions reported

Dry cough was present in 15/24 (62.5%) of those who had an adverse reaction to ACEI, and a patient had passage of loose stools, excessive micturition was seen in 19/26 (73.1%) of the patients on diuretics, while 11/25 (44%) of the patients on CCB (either as monotherapy or in combination) complained of increased frequency of micturition to their medicines distinct from an increase in volume (polyuria) seen with diuretics. The reactions are also documented in Table 2. The system organ classification is shown in Table 3, renal and urinary disorders being the most commonly reported system. Following the development of adverse reactions in these 93 patients, 46 of them (49.5%) discontinued their medicines with five of them substituting with another brand while 30 (32.2%) reduced their doses; however, 17 (18.3%) took no action [Table 2].

Adverse reactions: Symptoms checklist

With the administration of a modified symptom checklist to determine drug-related symptomatology in all the patients, 405 (78.8%) had adverse reactions related to the use of their medications. The frequency of micturition, poor erection, headaches, and reduced sexual urge were the symptoms most related to drug use with 37.7%, 25.7%, 22.6%, and 21.2%, respectively. The frequencies of the other symptoms are elucidated in Table 4.

Serious adverse reactions: Notable in this outpatient-based study was the absence of serious adverse reactions as there were no deaths, hospitalizations, disabilities, or life-threatening events that required intervention to prevent permanent damage.

Discussion

There is a need to define the present profile of antihypertensive medicines by finding out the present pattern of ADR which

Table 1: Distribution of the number of antihypertensive medicines used by the 514 patients and frequency of adverse reactions experienced

Antihypertensive medicine	Number of patients	ADR experienced, *n* (%)
1	67	10 (14.9)
2	142	18 (12.7)
3	137	21 (15.3)
4	113	32 (28.3)
≥5	55	12 (21.8)

χ^2=12.460, df=4, *P*=0.014 (significant). ADR=Adverse drug reaction

Table 2: Adverse reactions experienced by patients to antihypertensive medicines and actions taken by the patients following the reactions

Frequency of medicine class	Adverse reactions experienced (*n*)	Frequency (%)	Action was taken by patients
Calcium channel blockers (*n*=362)	Frequent micturition - 11, dizziness - 5, headaches - 5, others - 10	25/362 (6.9)	Dc - 10, reduced dose - 11, none - 4
Angiotensin converting enzyme inhibitors *n*=278	Dry cough - 15, dizziness - 2, diarrhoea, abdominal pain - 2, others - 5	24/278 (8.6)	Dc - 14 , reduced dose - 6, none - 4
Diuretics (*n*=273)	Excessive micturition - 19, dizziness - 5, headaches - 3, others - weakness, insomnia	26/273 (9.5)	Dc - 14, reduced dose - 9, none - 4
Beta blockers (*n*=118)	Dizziness - 1, dry lips - 1, cramps in foot - 1, abnormal sensation in head - 1	4/118 (3.4)	Dc - 1, none - 3
Centrally acting (*n*=95)	Dizziness - 4, headaches - 3, weakness - 5, others - 5	12/95 (12.6)	Dc - 7, reduced dose - 2, none - 2
Alpha blockers (*n*=9)	Dizziness - 1, dryness of legs - 1	2/9 (22.2)	Reduced dose - 2

Dc=Discontinuations

Table 3: The system organ classifications (Medical Dictionary for Regulatory Activities) of the reported adverse reactions by the hypertensive patients

System organ classification (MedDRA)	Frequency (*n*)
Renal and urinary disorders	32
Respiratory, thoracic and mediastinal disorders	16
Nervous system disorders	17
General disorders and administration site conditions	12
Cardiac disorders	12
Gastrointestinal disorders	5
Reproductive system and breast disorders	5
Musculoskeletal and connective tissue disorders	2
Skin and subcutaneous disorders	2
Eye disorders	1
Psychiatric disorders	1

MedDRA=Medical Dictionary for Regulatory Activities

may be peculiar to our environment. The study showed that a high proportion of patients have adverse reactions to their antihypertensive medications and the higher the number of medicines used the more the adverse reactions seen, as observed in a study by Lip and Beevers.[21]

Adverse reactions to medicines are an important consideration in the management of patients with hypertension as 50% of the patients who developed an adverse reaction discontinued their medicines. This finding was also seen in other studies on why patients discontinue their therapy.[13,22] In assessing the causality of the ADR, most of the reactions were adjudged to be ADRs. However, a few patients had ADRs that were adjudged to be unlikely and conditional using the WHO causality assessment algorithm. Although the algorithms improved the ability to characterize the relationship between suspected medicines and the ADR, patients and health-care providers are encouraged to report all cases of adverse reactions even when they are uncertain about the probability as this expands the database of ADRs.[23] The frequency of ADRs appeared to be higher in males, although was not statistically significant. It has been suggested that the female sex may be a risk factor for the development of ADRs due to possible pharmacokinetic differences.[24] The use of the medicine induced symptom checklist was to improve the reporting of patients who may have symptoms associated with the use of their medicines and cannot recall on questioning. Different studies have used this method though modified in this study; it also showed that a high proportion of patients had symptoms that they attributed to their medicines.[16,17,25]

The frequency of erectile dysfunction reported was more following the use of the symptom checklist. Many patients attribute sexual dysfunction to their antihypertensive medicines,[26,27] therefore adherence to these medicines may be poor due to their perceived adverse effect. Assessing the frequency of this complaint using a checklist or questionnaire has been shown to be helpful.[26,27] It may have also contributed albeit indirectly to more males reporting adverse reactions on direct questioning. The proportion of patients who had ACEI induced cough in this study was higher than shown in other studies.[28,29] The patients who used diuretics complained of excessive micturition; this had a serious impact on the patient's therapy as diuretics accounted for the highest number of reactions reported. The excessive micturition seen with diuretics may be due to the dose of diuretics, especially hydrochlorothiazide available in this environment. A study carried out in the North Central part of Nigeria also showed diuretics accounting for the highest rate of discontinuations to therapy.[30] Of interest were the reports of increased frequency of micturition following the use of CCBs. As distinct from the excessive micturition with diuretics, the CCB account for increased frequency (number of times) not reflected in the volumes of urine passed. This was observed early following the introduction of the CCBs.[31,32] This finding need to be further investigated as it was also seen using the MedDRA[18] system organ classification that the renal and urinary disorders had the highest frequency. We equally note the development of dizziness and dryness of legs to alpha blockers, (though infrequently used in this study) two of the users (22%) had adverse reactions, the reactions observed may be related to the orthostatic hypotensive effect of alpha blockers.[33]

Noticeable in this study, was the absence of reports of ADR to the ARBs. A reduced frequency has also been seen in another

Table 4: Frequency of symptoms attributed to medicine use in the 514 hypertensive patients using the modified symptoms checklist

Symptom	*n* (%)
Frequency of micturition	190 (37.0)
Poor erection	65 (25.7)
Headache	116 (22.6)
Reduced sexual urge	109 (21.2)
Insomnia	95 (18.5)
Weakness	95 (18.5)
Nightmares (bad dreams)	82 (16.0)
Coughing	79 (15.4)
Fatigue/little initiative	74 (14.4)
Swollen ankles/oedema	71 (13.8)
Muscular cramp/myalgia	70 (13.6)
Dizziness upon standing up	65 (12.6)
Palpitation	60 (11.7)
Warm feeling/flushes in the face	55 (10.7)
Dryness of mouth	45 (8.8)
Impotence	13 (7.3)
Other dizziness (unrelated to posture)	35 (6.8)
Disturbance of taste	25 (4.9)
Constipation	20 (3.9)
Depressed	20 (3.9)
Rash/itching	19 (3.7)
Nausea	19 (3.7)
Dyspnoea	17 (3.3)
Cold hands/feet	15 (2.9)
Urinary incontinence	11 (2.1)
Nervous/restless	9 (1.8)
Diarrhoea	6 (1.2)

review,[9] and ARBs have also been shown to have a good tolerability profile.[34]

Conclusions

In all, there is a relatively high prevalence of adverse reactions experienced by patients on antihypertensive therapy resulting in a high rate of discontinuations as seen in this study. Notable reactions experienced by the patients include dry cough to ACEIs, excessive micturition to diuretics, and frequent micturition in patients on CCBs. Utilization of a medicine induced symptom checklist revealed symptoms which were not reported on direct questioning such as reduced libido and erectile dysfunction.

Some knowledge of the profile of antihypertensive medicines in use by the physicians will aid the management of hypertension. Further studies are required to characterize this problem.

Acknowledgments

We would like to thank the University of Benin Teaching Hospital management and members of staff of the Department of Medicine and the consultant outpatient department for their assistance. We would also like to thank the patients who participated in this study. This study was self-funded and there are no potential conflicts of interest.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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GENERAL DISCUSSION

General discussion

This series of studies appears to have been the first to have evaluated the status of pharmacovigilance at teaching hospitals using the WHO core pharmacovigilance indicators in a geo-political zone n Nigeria. It confirmed the existence of structures and outlined the weaknesses of a growing pharmacovigilance system. It also presents a comprehensive review of the knowledge, attitude and practice of a large group of healthcare professionals towards pharmacovigilance. This study also seemed to have been the first to carry out an intervention at the institutional level on pharmacovigilance towards improving perception of pharmacovigilance among healthcare professionals as well increasing the number and quality of adverse drug reaction reports from the zone.

Pharmacovigilance in Nigeria- an Overview

The article approached the Nigerian pharmacovigilance scenario, defining the players, the governance structures and existing legislature. It also highlighted the absence of data to describe the magnitude of pharmacovigilance activities in the South-South zone of the country. The article addressed the issues pertaining to pharmacovigilance that may have been peculiar to persons living and working in a resource poor setting in sub-Saharan Africa. It also showed that the ADR profile of various medicines used in the setting were derived mostly from case reports and single stand alone studies. There appeared to be few studies describing the general profile of ADR reports from a geo-political zone in Nigeria.

Nigeria had the foresight to develop a stand-alone pharmacovigilance policy partly due to the recognition that poor attention to drug safety issues had wreaked some havoc in Nigeria with some notable issues such as the contamination of medicinal products with diethylene glycol that resulted in fatalities[1]. This article also showed the achievements of the pharmacovigilance system in Nigeria with creation of zonal centres, development of policy documents, development of alternative reporting mechanisms and public awareness regarding drug safety. Furthermore, the National Pharmacovigilance Centre has also carried out some active surveillance on medicines of public health importance as well as training healthcare professionals. The National Pharmacovigilance Centre also receives ADR reports directly from marketing authorisation holders as well as from other institutions that carry out pharmacovigilance activities in the adjusted organogram. The study identified that in-spite of the above encouraging activities; the number of reports was still sub-optimal and partly attributed to a poorly understood reporting process, poor institutionalisation and dedication to pharmacovigilance, insufficient funding and insufficient pharmacovigilance experts. All these may have hindered a more rapid growth of the system.

The contributions of irrational pharmacotherapy and quality issues to drug safety concerns found in the setting were notable. It was also noted that there was a lack of data on drug related safety issues, thus warranting the need to further explore the activities in the hospitals.

Assessment of the state of pharmacovigilance using the WHO Core Pharmacovigilance Indicators.

Study II addressed the status of pharmacovigilance in teaching hospitals. This is the first published work in this setting that assessed the pharmacovigilance system at the level of the teaching hospitals. The WHO pharmacovigilance indicators were developed to ensure that national pharmacovigilance centres had indicators first for self assessment to ensure growth and as well prevent stagnancy. It was also designed to assess comparatively, individual aspects of pharmacovigilance in order to develop interventional strategies for each centre. The structural indicators highlighted deficiencies regarding physical space, infrastructure, personnel and funding. The quantitative representation of the process, outcome and impact indices allowed for the determination of the burden of pharmacovigilance in this resource constrained setting. This allows for the use of the indicators to identify gaps in the PV system, improve the PV network in the field and provides a model for establishing such a network. In this study, the indicators identified various deficiencies including but not limited to low level of reporting, poor record keeping which rendered computation of the drug related morbidities difficult. Furthermore, measures of outcomes and the impact of PV activities were essentially low; for instance, there were minimal signals documented, safety decisions conveyed from PV activities were negligible.

Assessment of the teaching hospitals in the zone is otherwise serving as a model for which to lay a foundation for future works. Also the National drug policy and the national pharmacovigilance policy[2,3] had suggested in the implementation frameworks that health institutions should have their own pharmacovigilance mechanisms. No metric had been used prior to this time to ensure compliance with the policy. The use of the WHO indicators was aimed at filling this gap and also to provide the centres with a document that may aid PV in those centres unaware of the policy documents.

It was also shown that of the six of the teaching hospitals visited; only three could be described as partially or fully functional. The ADR reports were mostly concentrated in one centre which also was the only centre with financial provisions for pharmacovigilance. Institutional challenges that were encountered included the relative absence of a drug therapeutic committee (DTC) in the hospitals, non availability of standard ADR reporting forms, and reports regarding the broadened scope of pharmacovigilance. These are very important factors that impact on ADR reports as studies have shown that for institutions to have a successful regulation of medicines, quality control measures, an oversight committee such as the DTC distinct from the hospital management ought to be in place[4]. Further, there was inadequate documentation of patients' records that were needed in order to calculate the impact/outcome indicators. We demonstrated the need for evaluation of a pharmacovigilance system in teaching hospitals was key towards improving the PV system both at the zonal as well as the national level. The WHO core pharmacovigilance indicators however only described the presence or absence of some of the structural indicators and not the overall functionality of the system. Additional points raised during the interviews of the persons in the various pharmacovigilance committees revealed some of these deficiencies, such as inadequate staffing for the pharmacovigilance centres with most centres having part time staff that were involved in other activities, lack of training for the PV staff, absence of feedback from the NPC on previous ADR reports sent, infrequent notifications on drug related events from the NPC, irregular meetings of the PV committee as well as inadequate space for PV. There was also lack of reference text and other materials, poor hospital internet connectivity to undertake pharmacovigilance

activities and inability to provide current and up to date drug information to staff in the centres. We recommend that regular (at least twice yearly) evaluation of the PV systems in teaching hospitals be conducted, that PV systems and indeed the hospital health systems be strengthened financially and also that more attention be paid to staffing and ensure capacity building of PV staff. That particular scoring metrics and reference benchmarks be developed for the WHO core pharmacovigilance indicators to further help the evaluation of functionality of budding PV systems.

Overall, it helped determined the deficiencies in the PV system in the teaching hospitals and these could have an over-arching effect due to the training of undergraduate and postgraduate students in most cadres of health care professionals being undertaken in the hospitals.

Drug utilisation pattern in South-South Nigeria

In determining the challenges besetting a pharmacovigilance system, it is important to assess the use of medicines as this may explain pattern of ADRs observed in the setting and provide a rationale for a comprehensive approach in reducing the burden of drug related events.

This study evaluated the contribution of irrational use of medicines especially the prescribing patterns of physicians in the zone and the possible influences it may have on pharmacovigilance. The WHO had estimated that irrational use of medicines is a global problem and this is related to polypharmacy, improper use of antimicrobials, over prescribing and use of injections when not indicated, non-adherence to established clinical guidelines in case managements, as well as prevalent self medication practices and non adherence to medication plans and dosing regimens[5]. Development of antimicrobial resistance is promoted by irrational drug use and this may be prevalent in our setting with its high burden of communicable diseases. Therefore knowledge of the use of medicines in any community aids the development of strategies that can mitigate the attendant consequence of irrational use.

It was observed in this study that there was still a high prevalence of polypharmacy, and non adherence to the EML, also there was still a high rate of prescribing with the brand names of the medicines. These portend doom for a growing pharmacovigilance system as the risk of adverse drug reactions increase with an increasing number of drugs, increased possibilities for medication errors in dispensing and self administration as a previous study had shown that patients may use two different brands of same medicines due to brand prescribing (patients used different brands of arthemether-lumefantrine and another used different brands of Nifedipine)[6] there is also an increased risk of drug-drug interaction[7]. Again the increasing prevalence of hypertension may have contributed to this high rate of polypharmacy as it is generally recommended to use 2 or more medicines rather than increasing the dose of a monotherapeutic agent when a patient is not at the recommended goal for blood pressure control[8]. We also noted a lot of vitamin prescriptions contributing to the burden of polypharmacy in this study. While multivitamins, mineral supplements are generally regarded as safe and available as OTC medications, potentials for interactions and ADRs has been shown to occur following the use of multivitamins[9].

Rational prescription of antibiotics may reduce the burden of antimicrobial resistance especially in a setting where the health system is not adequately equipped to provide alternative amtimicrobials and also since most patients pay out of pocket for medicines in Nigeria, an increased incidence of antimicrobial resistance will translate to increased

economic challenges to an ailing health system. The use of antibiotics in this study was found to be lower than from previously developed optimal values[10].This suggests that for patients presenting to the hospital for care, there appears to be a better performance of the prescribers regarding prescription of antibiotics and may indicate a gradual understanding of the need to use antibiotics rationally

It was also encouraging to find an optimal use of injections in most of the centres in the South-South Zone. This may mean a reduction in the risk of injectable associated infections and ADRs. It may also mean that prescribers are gradually becoming more adherent to rational prescribing of injections. This might also be attributed to the paradigm change in antimalarial prescribing from mainly injectables to the use of the oral ACTs [11] although a case still needs to be made for interventional strategies in the management of malaria as most of the injections prescribed in this study were for antimalarials. The recommended method of treatment for malaria is oral ACTs and injections are recommended for use in those with severe malaria[12]. We recommend that continuous medical education be given to prescribers in the zone on the management of malaria and rational use of injectables in line with the present STG and malaria guidelines.

Most of the available safety profile studies on medicines that were commonly prescribed in this study are in the Caucasian population[13–16] and very few studies in the homogenously black population in Nigeria. Lack of accurate statistics regarding qualitative and quantitative drug utilisation may have hampered this development. This was noted as a limitation of this study as we were unable to link prescriptions and usage to patient's demographics. We therefore recommend that measures be put in place for development of the health information systems with a view towards computerisation, and also developing a database that may allow adequate evaluation of the ADRs that may occur following the use of these commonly prescribed medicines.

To further examine the state of pharmacovigilance in the teaching hospitals, we also decided to inquire from the Healthcare Professionals in study IV, their knowledge, attitudes and practice relating to pharmacovigilance.

Knowledge, Attitude and Practice of health professionals regarding Pharmacovigilance in South-South Nigeria.

Following the evaluation of the PV systems, it was obvious that ADR reports were very few in most of the centres visited and multiple reasons were proffered such as lack of knowledge and awareness of pharmacovigilance, insufficient ADR forms, fear on the part of the personnel about possible consequences of reporting ADRs, inter-professional rivalry among healthcare professionals,

We therefore sought to know what the awareness, perception, and practice of the healthcare professionals who can report ADRs (namely doctors, pharmacists and nurses) were towards pharmacovigilance.

The knowledge, attitude and practice of healthcare professionals working in teaching hospitals in the south-south zone towards pharmacovigilance had not been previously explored despite the finding that there exists some differential level of pharmacovigilance activities at the various institutions. Some preliminary studies carried out in Nigeria focused on single institutions and mostly on physicians[17–22]. The broadened scope of pharmacovigilance has also not been related to the reports in the database.

The choice of teaching hospitals was to allow for inclusiveness of most clinical disciplines and a wide access to various types of patients. Furthermore, the use of a semi structured questionnaire was to allow for participants give their views regarding the subject and identify gaps in knowledge not covered by the closed ended questions.

The study revealed a modest knowledge of pharmacovigilance especially regarding concepts such as reporting mild ADRs, reporting delayed ADRs and ADRs occurring at the end of use of a medicinal product. Cases of drug abuse, drug dependence and medication errors were also less likely to be reported. These are important areas in pharmacovigilance that highlight noxious and unwanted nature of medicines. This implies that healthcare professionals require more information regarding reporting less commonly known safety concerns. As shown in the study by Ogunleye et al, mediation errors are also less likely to be reported by healthcare professionals in Nigeria[23]. Other questionnaire based studies in other parts of the world had also shown that HCP were more likely to report serious ADRs, ADRs relating to new medicines and very few HCPs had reported with the authorized ADR forms[24–26].

The reasons adduced for poor reporting of adverse reactions in this study were related to the risk of possible litigation, threats to career and life, difficulty in determining ADR occurrence due to polypharmacy by patients, use of herbal medicines, loss of monitoring and lack of training among others. Attitudinal problems such as ignorance have been ascribed as likely causes of underreporting[27]. This was also found in this study. The self reported practice of reporting ADRs in this study was equally low and this was reflected in study III showing very few reports in the database of the various institutions and some not at all. Again, we found that more nurses used the ward report book to report ADRs. Due to the nature of their work, nurses may be the first to observe ADRs and are required to document the patients' problems in the ward report book for every shift[28]. The ward report book could be an avenue for ADR surveillance in this setting, and although nurse's self reported utilisation of the yellow form was very poor, they could be encouraged to use the national ADR form. Inadequate knowledge of pharmacovigilance and poor utilisation of the ADR form by nurses has also observed in other studies[29,30]

This study also revealed factors that hampered the processes of reporting ADRs in the various institutions and this again could be explained by the poor PV system that obtained in most of the hospitals visited, and factors associated with reporting ADRs using the national ADR form included the male sex, being a pharmacist, and previous training. It can be adduced that perhaps due to the emphasis on different aspects of pharmaceutical processes and medicine use during their undergraduate training, pharmacists may have had more formal training on the use of the national ADR form. We recommend that training on PV, increased awareness and development of easier reporting systems to enhance ADR reporting be carried out in the teaching hospitals. At the time of the study, electronic reporting was not available in Nigeria and in view of the developments in web based applications in pharmacovigilance in other climes and the increasing availability of smart-phone and internet services among healthcare professionals, the respondents were asked if the internet could be useful in reporting ADRs and about 48% would prefer to report ADRs via the internet. Some had also proffered that an e-version of the form may encourage them to report ADRs. This suggests that uptake of ADR e-reporting may be high in Nigeria when introduced.

We also recommend that increased emphasis on pharmacovigilance may be needed during undergraduate studies and other informal training schemes such as orientation programs to

all cadres of healthcare professionals. The use of the International Society of Pharmacovigilance (ISOP) pharmacovigilance curriculum[31] will surely aid the implementation of such training schemes.

A misalignment existed between the proportion of Healthcare professionals who had reported an ADR and the numbers of ADRs reports found in the local pharmacovigilance databases, this could be ascribed to the possibility that those ADR reports were not submitted despite being filled, or poor record keeping resulting in misplaced reports in the various facilities may have contributed to the low number of reports seen. Again we cannot exclude recall bias on the part of the reporters as this was a self reported exercise. Of interest, this differential in the actual and perceived number of reports has been previously observed in the UK[32].

Educational intervention to improve knowledge, attitude and practice of pharmacovigilance of healthcare professionals in South-South Nigeria.

Following the baseline evaluation of the KAP of healthcare professionals in South-South Nigeria, an interventional randomised study was carried out and results obtained described in Study V. Study IV showed that in the South- South zone, the level of awareness of pharmacovigilance was still sub-optimal with the participants equally suggesting training as one of the ways in which improvement may be obtained. There had been no previous study in Nigeria that had combined an active educational seminar with a positive reinforcement reminders delivered via text messages on pharmacovigilance at the level of a geo-political zone. Other related interventional programs targeted focused areas such as the antiretroviral programs with limited sample sizes and mostly at single institutions[33]. In designing this intervention program, a theoretical domain framework was considered in relation to ADR reporting[34–36] and we also considered that a multifaceted interventional strategy suitable to our environment would achieve our aim[37–39] hence the use of the short messaging system in delivering the reminders.

Study V showed that the educational intervention followed by the reinforcement with text message reminders improved the healthcare professionals' awareness and practice of pharmacovigilance in the intervention arm. It also suggested that multifaceted educational interventions at the level of the institution could improve the pharmacovigilance system in the region. We recommend that continuous medical education be conducted on healthcare professionals, emphasis be laid on all aspects of pharmacovigilance including delayed ADRs, ADRs persisting for a long time, medication errors, cases of drug dependence and abuse. That newly marketed medicines and vaccines should be monitored closely by healthcare professional. The use of SMS reminders as a reinforcement tool could help in other intervention programs. Furthermore, continuous medical education targeting a change in attitude may need to be developed to effect longer lasting attitudinal change. Although there were a few limitations in the study, we attempted to mitigate them by trying to minimise contamination by delivering the lectures in institutions randomised to the intervention arm only, using a repeated cross-sectional design to allow for group level evaluation and reduce the impact of a possible large drop-out rate[40,41]. Furthermore, the sensitivities of being targeted by the respondents necessitated a re-sampling from the same population in the post-intervention assessment evaluation obviating a more direct pre-post approach. The consent obtained was based on complete anonymisation and this was also a limitation of the study.

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Impact of an educational intervention on adverse drug reaction reporting in tertiary hospitals in South-South Nigeria

ADRs have been shown to be a major cause of morbidity and mortality worldwide[42–44] and the addition of non-communicable diseases especially hypertension to the prevailing communicable disease burden in Nigeria magnifies the health issues in this setting. In Nigeria, the beneficial effects of medicines are often emphasised with fewer reference to the harmful effects that may ensue from it. Earlier related research in Nigeria, in terms of sequence and chronology, focused on affordability, availability and quality of medicines related problems. However, there has been a dearth of studies describing the adverse reactions profile found in Nigerians. This is in-spite of studies that outlined the genetic polymorphisms that may accompany ADRs and the subsequent need for personalised medicines based on the profile[45,46].

Therefore in the study VI of this thesis, the aim was to evaluate the impact of an educational intervention and SMS reminders on the number, quality and profile of ADR reports in this geographical zone. This was to enable description of the ADRs to commonly used medicines in the zone. The study had the aim of training a high number of healthcare professionals, and to have an unbiased evaluation of the type of reports emanating from the centres. Furthermore, the educational seminar centred on the important domains already described. It tried to explain the foundation for drug safety in the Nigerian context and the reporting processes. It also made available the contact details of the local pharmacovigilance contact persons in order to improve access to the forms. Frequently asked questions and the algorithm of reporting any suspected ADR were equally expatiated.

The study focused on describing the ADR to commonly prescribed and used medicines such as anti-infectives, antimalarials, analgesics, anti-inflammatory and antihypertensive medicines. Again, another facet that was explored in this study was about the quality of the completed adverse reactions. There are various aspects to defining quality in pharmacovigilance and it has been suggested that from collection to transmission to the database, there is a need to apply quality control measures in order to have usable data[47]. ADR forms with completely filled fields were also evaluated in this study as a measure of quality of the forms. In this study, we showed that reporting of adverse drug reactions in teaching hospitals is generally low, that anti-infectives especially antiretroviral medicines and antibacterials were the most implicated medicines causing the ADRs being reported. This was not unexpected considering the burden of communicable diseases in Nigeria, and also the antivirals for systemic use (Highly Active Antiretroviral Therapy- HAARTs) are given freely or heavily subsidised. The donor agencies make ADR reporting a part of their routine evaluation, thus this may have been partly responsible for the high number ADRs attributed to HAARTs. We also found that there appears an increased trend towards reporting the development of ADRs to medicines acting on the renin-angiotensin system as well as ADRs involving the use of multiple medicines.

Furthermore, overall reporting of ADRs, the level of completeness and reporting of valid ADRs and reporting of ADR in children and adolescents appeared to have improved after the educational intervention and reminders. There were only five ADR reports by nurses in the study and they were all from a single centre, and doctors reported more cases of serious ADRs. We recommend that increased emphasis be laid on the curriculum development and

education of nurses in using the ADR form to report, there may be a need to further evaluate the use and pattern of ADR to, antiretroviral medicines and medicines acting on the renin- angiotensin system, that there is need for increased research into the pharmacogenetics of these medicines used in Nigerians. Again, the present national ADR form may require revision to improve ease of reporting and increased awareness and training be carried out to improve the quality and number of reports.

The limitation to this study was the lack of a comparative control group as the hospitals had been randomised prior to evaluation of the system but a before and after study design was also helpful in determining the effect of the intervention. Again, the sizes of the hospitals could not determine the level of pharmacovigilance activity as the only centre where nurses had reported was a medium sized hospital compared to a larger hospital that had no ADR report prior to the intervention. Pharmacovigilance is a new concept in Nigeria with significant institutional and professional mistrust and suspicions about adverse drug reaction reporting. The culture of reporting adverse drug reactions had not been established in Nigeria which makes evaluation of reports to the National Pharmacovigilance Centre unhelpful. It was to espouse the issues around this problem that informed conceptualisation of the study. Again, there is a basic assumption that the health professionals were mainly trained in Nigeria using the same curriculum and the terms of engagement into the hospitals for service and further training are similar having been set by government. There may be inadvertent disparities which may arise from institutional peculiarities such as attrition rates in fellowship examinations. In this regard, the fellowship program is quite dynamic and there could be significant changes following the examinations following exits of the staff from the hospital. Also, there may have been some pharmacovigilance activities in the some of the non-intervention hospitals prior to the study. Industrial disruptions in the Nigerian health sector during the study period may have also contributed adversely to the few number of ADR reports obtained in the study. However, these reflect the practice in a resource constrained setting with attendant system challenges and may not be peculiar to pharmacovigilance.

In a population with an increasing burden of non-communicable disease, hypertension with a prevalence rate of 28.9% [48]poses a significant burden on health services and as such antihypertensive medicines presents an area for identification of adverse reactions in this homogenous population. Also the perception of the patients about the ADR or symptoms related to their antihypertensives is relatively not well known. The consequences of non-adherence to antihypertensive medications are also well known. Study VII examined the ADR profile as well as the patient's perspective of medicine related symptoms using a checklist in order to characterise the ADR to this broad class of medicines and identify areas where future interventions might be needed.

A profile of adverse effects of antihypertensive medicines in a Tertiary Care clinic in Nigeria

This study was intended to address the ADRs in a clinical area where medicines are used on a chronic basis in the treatment of hypertension. It highlighted the adverse effects experienced by patients on antihypertensive medications. It therefore focused on patients' ability to recognise and report ADRs as well as the ability of the clinician to identify these untoward events. This was carried out using a double pronged approach by asking targeted questions with the aid of a semi-structured open ended questionnaire and a standard tool - the modified symptom check list. This further assisted patients to address areas bordering on disclosure patterns and non-reporting of ADRs. We discovered that ADRs relating to sexual function were now disclosed on close questioning with the use of the modified checklist, this approach may be useful in clinical practice in Nigeria as such ADRs adherence. This was also reported in another study[49].

As an additional method of increasing the number of ADR reports, patients are encouraged to report their ADRs or any medicine related symptoms either to the healthcare professional or directly to the pharmacovigilance centres and this has significantly increased the reports in the pharmacovigilance databases[50–52]. The method utilised in this study may be encouraged and broadened to include other disease entities. Other studies in the setting have also followed up patients with phone calls to enquire about the ADRs experienced[53]. However, there may be challenges sustaining such a method. We recommend a two pronged approach (direct questioning and use of a check-list) in assessing the development of ADRs in ambulatory patients with chronic diseases in our setting due to the high proportion of discovered possible drug related effects and negative impact on adherence that was observed in this study.

This study also highlighted possibility of racial influences on adverse reactions as shown by the high number of angiotensin converting enzyme inhibitors induced cough in Blacks which has been alluded to in a previous study on development of ACEI induced cough in Nigerians [54]. There still exists a dearth of data on the safety profile of commonly used medicines in Nigeria. A limitation of the study was the inability to relate all reported medicine related symptoms to their antihypertensives. However, in view of the negative effects it had on the patients' adherence to their antihypertensive medicines, we still feel the utilisation of the symptom check list may be useful in our setting. We also noted that absence of serious ADRs in this study, this is probably due to the ambulatory nature of the study and those who may have had serious ADRs may have presented to the emergency department for care. There are very few studies that have actively sought out the patients' report regarding the development of ADRs on their antihypertensive medications in our environment. These tools may be useful in contributing to the growth of the pharmacovigilance system in Nigeria.

Limitations

The studies have been carried out under difficult circumstances in a setting where issues regarding drug use and its safety are not prioritized. The mindset of the population is that medicines are beneficial and addressing cautionary issues of safety is regarded with suspicion. However, the study appears to be a wake- up call to gear the various stakeholders to addressing safety issues.

- A number of participants in the study at the initial stage were unwilling to provide consent and viewed the study with suspicion.
- The record keeping in the hospitals was poor thus more time was required to obtain data.
- The logistics of the across country visits to the various centres which spanned about a 1000km posed a challenge. Again, labour issues with industrial strikes by working staff necessitated unplanned re-visits within the time frame set for the study.
- Internet facilities as well as network connectivity also posed a challenge since it was incumbent to obtain data at stipulated time.
- Inter-professional issues were of some consideration. Of interest, medical doctors deferred pharmacovigilance issues to pharmacists and nurses deferred issues to both medical doctors and pharmacists.

Conclusion and Recommendations

From this series of studies, it is evident that there exists a pharmacovigilance system in teaching hospitals in South –South Nigeria although functioning sub-optimally. Irrational medicine use especially polypharmacy, brand name prescribing, non adherence to the EML were some of the drug related factors identified as prevalent in the zone. The WHO Core pharmacovigilance indicators also outlined inadequate structures for pharmacovigilance, rudimentary processes as well as absence of records to compute the outcome/impact indicators. Despite the challenges experienced, the study was carried out providing very useful information and being foundational will serve as a reference point as pharmacovigilance grows to maturity over the years, not only in the South-South zone but for the country at large.

The collaboration between academia and the regulatory agency in pharmacovigilance is a synergistic one where pharmacovigilance is strengthened with the availability of experts and also this could lead to improvement of the quality of reports. The involvement of the community was explored in chapter VII with the questionnaire based study using hypertension (a prevalent non-communicable disease in Nigeria) as a model to elucidate medicine related symptoms not previously reported by the patients. We believe these are workable models for pharmacovigilance in our environment.

Building a stronger health information system will be necessary and essential for the growth of the pharmacovigilance system. The involvement of all stakeholders with a lead from government and its regulatory agencies is of utmost importance. To address this, the following recommendations are therefore posited:

- The strengthening of the pharmacovigilance system in this region and thus the entire country is of great importance and government should take leadership in putting the necessary framework and enabling environment with adequate networking and integration into the healthcare system.
- Awareness creation and sensitization of all stakeholders should be of urgent priority. The appropriate organs of government should embark on a strong advocacy to all stakeholders notably legislature, academia, healthcare professionals, policymakers, health managers, consumers, etc.
- There is a need to put in place enabling policies, laws and regulations so as to ensure a clement environment for drug use and PV activities guaranteeing their sustainability.
- Academic and professional curricula should incorporate PV and rational use of medicines so as to prepare potential graduates to address drug related problems.
- Appropriate strategies are needed to ensure rational use of medicines –this can be driven by the establishment of a Rational Medicine Use Commission to support the Federal Ministry of Health (FMoH) and guide health care institutions as well as supporting the zonal and other pharmacovigilance centers hinged on a strong National Pharmacovigilance Centre.
- The FMoH through its organs should maintain a continuous educational activity on the effective and safe use of medicines and the reinforcement exercises should address lapses detected during monitoring and evaluation of the system.
- The teaching hospitals should ensure that the various specialists monitor drug related events in their various sub-specialties with a view to identifying and addressing safety concerns.

- The WHO Core pharmacovigilance indicators should be integrated into the health care system for the regular monitoring and evaluation of drug related activities and identified lapses within the system should be rectified.
- Electronic heath registries will be useful in obtaining the much needed safety data peculiar to this homogenous Nigerian population

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Appendix I: Consent Form and Questionnaire

KNOWLEDGE, ATTITUDE AND PRACTICE OF HEALTHCARE WORKERS IN THE SOUTH-SOUTH ZONE OF NIGERIA TOWARDS PHARMACOVIGILANCE

Dear Sir/Madam,
I am Dr. A. Olowofela, a Consultant Physician and Clinical Pharmacologist with the South-South Zonal Pharmacovigilance Centre in UBTH and I am conducting a study regarding the safety of medicines.
This questionnaire is aimed at determining the knowledge attitude and practice of pharmacovigilance by the health workers in the south -south zone of the country and it is hoped that this research will ultimately improve patient safety. Your participation is entirely voluntary, your privacy will be respected and your details will be kept confidentially and will not be disclosed to third parties.

You are unlikely to come to any harm in participating in this study and there will be no prejudices if you decline participation. By agreeing to participate in this study, you will be required to fill this questionnaire and you may receive emails, text messages from the South-South Zonal Centre on pharmacovigilance related news. The study will last for approximately 12 months with repeat surveys I will appreciate if you could spare 10-15 minutes to fill this repeat survey questionnaire.

The results from this survey will be published in local and international journals but your privacy will be ensured. You may be contacted after this survey, but if you do not wish to be contacted or receive any notification, kindly indicate in the form below. You should kindly return the completed questionnaire as soon as possible to the author.

If you have any questions regarding this survey and the study, you may contact me via email- felabimbola@yahoo.com, zpcsouthsouth@gmail.com or via telephone +2348037075435.

Thank you.

Dr. Abimbola Olowofela
MBBS, FWACP, FMCP,
Consultant Physician/ Clinical Pharmacologist,
Department of Medicine,
University of Benin Teaching Hospital,
Benin-City.

I have read and understood what the study entails and consent voluntarily to be a participant in this study.

Signature_____

Date_____

1**. What do you understand by the term ADVERSE DRUG REACTION (ADR):**

……

……

.....

.....

2. An ADR can : (Multiple options can be ticked)

a.	Result from the pharmacological actions of the drug.	Ye s [ ];No [ ]; I don't know [ ]
b.	Be a new and unexpected reaction to the drug	Yes [ ];No [ ]; I don't know [ ]
c.	Persist for a long time	Yes [ ];No [ ]; I don't know [ ]
d.	Be delayed for years	Yes [ ];No [ ]; I don't know [ ]
e.	Occur at the end of use of the medicine	Yes [ ];No [ ]; I don't know [ ]

3. ADR reports should be submitted if the drug is (Multiple options can be ticked)

a.	A newly marketed medicine	Yes [ ]; No [ ]; I don't know [ ]
b.	An established medicine and vaccine	Yes [ ]; No [ ]; I don't know [ ]
c.	Herbal medicine	Yes [ ]; No [ ]; I don't know [ ]
d.	Biological medicine	Yes [ ]; No [ ]; I don't know [ ]
e.	Complementary medicine	Yes [ ]; No [ ]; I don't know [ ]
f.	Vaccine	Yes [ ]; No [ ]; I don't know [ ]
g.	Over the counter preparation (OTCs)	Yes [ ]; No [ ]; I don't know [ ]
h.	Used by children	Yes [ ]; No [ ]; I don't know [ ]
i.	Misused or used with error	Yes [ ]; No [ ]; I don't know [ ]
j.	Used in cases of drug abuse	Yes [ ]; No [ ]; I don't know [ ]
k.	Used in cases of drug dependence	Yes [ ]; No [ ]; I don't know [ ]

4. ADRs should be reported only if they are: (Multiple options can be ticked)

a.	New	Yes [ ]; No [ ]; I don't know [ ]
b.	Known	Yes [ ]; No [ ]; I don't know [ ]
c.	Unexpected	Yes [ ]; No [ ]; I don't know [ ]
d.	Mild	Yes [ ]; No [ ]; I don't know [ ]
e.	Life threatening	Yes [ ]; No [ ]; I don't know [ ]

5. Who should report an ADR? (Multiple options can be ticked)

a.	Medical doctors	Yes [ ]; No [ ]; I don't know [ ]
b.	Nurses	Yes [ ]; No [ ]; I don't know [ ]
c.	Pharmacists	Yes [ ]; No [ ]; I don't know [ ]
d.	Others (specify)……	

6. Are you aware if a local pharmacovigilance centre or committee is available in your hospital?

Yes [ ]; No [ ]; I don't know [ ]

6a: If yes: have you ever visited the centre or contacted the committee? Yes[ ]; No[ ]

7. Are you aware of the existence of south-south zonal pharmacovigilance centre? Yes[ ]; No[ ]

8. Are you aware of the existence of the National Pharmacovigilance Centre Yes[ ]; No[ ]

9. If yes, State the location of the National Pharmacovigilance Centre...……

1**0. Are you aware that the Nigerian National Pharmacovigilance Centre has edited an ADR reporting form (yellow form) for reporting ADRs?** Yes [ ]; No [ ]; I don't know [ ]

11. Have you ever seen the adverse drug reaction reporting form (yellow form)? Yes [ ]; No [ ]

12. What are the important elements in the ADR reporting form (yellow form) in reporting an ADR, (Multiple options can be ticked).

a. Suspected drug [ ] b. Suspected reaction [ ] c. Patient details [ ] d. Reporter details [ ]

Attitudes

13. Do you believe you should report all ADRs whatever the information you have?

Yes [ ]; No [ ]; I don't know [ ]

14. Do you find it difficult in determining if an ADR has occurred? Yes [ ]; No [ ];Sometiimes [ ]

If yes, Why? List the most likely reasons.....

.....

15. Do you feel you should report all ADRS even when you are not sure it is drug related?

Yes [ ];No [ ]; I don't know [ ]

16. Do you find it difficult to report because you feel it won't make a difference in contributing to medical knowledge? Yes [ ]; No [ ]; Sometimes [ ] I don't know [ ]

17. Do you feel you should receive incentives for reporting? Yes [ ]; No [ ]; I don't know [ ]

18. Do you feel you have a professional obligation to report ADRs? Yes [ ]; No [ ] I don't know [ ]

19. Do you think ADRs reporting should be made mandatory for all health care workers in Nigeria?

Yes [ ]; No [ ]; I don't know [ ]

20. If yes, which category of health workers? (Multiple options can be ticked)

Doctors[ ], Dentists [ ], Pharmacist [ ], Nurses[ ], Others [ ]

21. Do you feel reporting ADRs puts your career at risk. Yes [ ]; No [ ]; I don't know [ ]

21a: If Yes how?.....,,,,,,,,,,,,,

22. Do you feel ADR reporting should only be for the benefit of publishing an article?
Yes [ ]; No [ ]; I don't know [ ]

Practice

23. Have you ever observed an Adverse Drug Reaction? Yes[ ]; No[ ];
24. Have you ever reported an Adverse Drug Reaction? Yes [ ]; No [ ];
if NO please go to question 33.
24a. If Yes? What was used in reporting the ADR ?
Yellow form [ ], Case Note [ ], Ward report book [ ],
Others (Please specify.....

25. Have you ever filled an ADR reporting form (yellow form)?

Yes [ ]; No [ ]; I don't know [ ]
26. Where did you send your filled out form to?

National pharmacovigilance centre in NAFDAC [ ];
Local pharmacovigilance centre [ ];
Others(please state)……..
27. How many ADR reports did you submit in the last year? (Please specify the approximate number)……
28. How many ADR reports did you submit in the last month? (Please specify the approximate number…….
29. What proportions of ADR have you seen and not reported(Please estimate approximate value)
<10%[ ], 11-29%[ ]30-50%[ ]; 51-70%[ ] 71-100% [ ];
30. Do you find it easy accessing ADR forms in your centre? Yes[ ]; No[ ].
30a. Please give reasons for your answer……..

……

31. Do you find reporting with the yellow form easy? Yes [ ]; No [ ];
31a. Please give reasons for your answer……..

……
……

32. How would you describe the process of returning the filled ADR forms in your centre?
Extremely difficult [ ]; Difficult [ ]; Neutral[ ]; Easy[ ]; Very easy[ ]
33. Have you received any training on adverse drug reaction reporting?
Yes [ ]; No [ ]; I don't know [ ]

34. What factors do you think can improve ADR reports in your centre- (please list)

……
……
……
……

35. Do you think filling the form on the internet would help you report more ADRs?
Yes[ ]No[ ], Not sure[ ]

36. Do you think filling the form by sending a SMS (text message) would help you report more ADRs? Yes[ ]No[ ], Not sure[ ]

37. Would having a direct access to the zonal pharmacovigilance centre through telephone help you report more cases and report faster? Yes[ ];No[ ]; Not sure[ ]

38. Would having a direct access to the zonal pharmacovigilance centre through email will help you report more cases and report faster? Yes[ ]; No[ ]; Not sure[ ]

39. What steps could you take when an ADR has occurred? (Multiple options can be ticked)

a. Stop medicine: Yes [ ]; No[ ]; I don't know[ ]
b. Reduce dose: Yes [ ]; No[ ]; Not sure[ ]
c. Notify the head of your team; Yes [ ]; No[ ]; Not sure[ ]
d. Record drug details: Yes [ ]; No[ ]; Not sure[ ]

40. Which sources do you use for drug information? (Multiple options can be ticked)

a. MIMS [ ];b. Standard textbooks [ ]; c. Internet [ ];

d. Standard formularies_ BNF, PDR. [ ];

e. Others (Please indicate_.....

DEMOGRAPHICS

41. Institution:
42. Age:
43. Gender:
44. Type of health care worker: Doctor[ ], Nurse[ ], Pharmacist[ ].
45. Rank:
46. Years of practice since graduation:
47. Department:
48. Unit/ Specialisation:
49. Ward: Medical[ ] Surgical[ ]Paediatrics[ ]Obst And Gynae[ ]Oncology[ ]
Hematology[ ] Others(please indicate)
……

50. Mobile Phone number:
51. Email address:
52. Would you like to be contacted via email or via telephone: Yes[ ]No[ ]

Thank you for your cooperation and time.

Appendix II: Ethical Approvals

NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL

NAFDAC CORPORATE HQ:
PMB 5532 Olusegun Obasanjo Way
Wuse Zone 7, Abuja
Tel: +234 9 6718509
E-mail: nafdac@nafdac.gov.ng
website: www.nafdac.gov.ng

LAGOS LIAISON OFFICE:
Central Laboratory
No 35 Oshodi Apapa Expressway
Lagos State
Tel: +234 1-4730643

Your Ref: ..... Our Ref: ..... Date: .....

NAFDAC/PV/P1/234/2. **17TH September, 2015**

Dr. A.Olowofela,
Consultant Physician/Clinical Pharmacologist,
Department of Medicine,
University of Benin Teaching Hospital,
Benin City, Nigeria.

Sir,

RE: NOTIFICATION OF PHARMACOVIGILANCE RESEARCH IN SOUTH-SOUTH ZONE OF NIGERIA.

Please refer to your request on the above mentioned subject matter dated 11th September, 2015.

I have been directed to convey the approval of the Director-General (NAFDAC) in respect to your request to carry out a "Pharmacovigilance Research in South-South Zone of Nigeria".

While appreciating your efforts towards generating scientific data for evidence based decision making, please accept the warm regards of the Director-General NAFDAC.

H. Nosiri

Pharm. (Mrs.) Helga Nosiri
For: Director General NAFDAC

RESEARCH AND ETHICS COMMITTEE

NIGER DELTA UNIVERSITY TEACHING HOSPITAL, OKOLOBIRI

CLEARANCE CERTIFICATE

Application form number: **NDUTH/ REC/ 0005/2015**

Project Title: **EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH NIGERIA.**

Investigators: **DR OLOWOFELA AMBIBOLA.**

Department/Institution: **CLINICAL PHARMACOLOGY & THERAPEUTICS, UBTH.**

Date considered: **7TH SEPTEMBER, 2015.**

Decision of the committee: **APPROVED.**

Chairman: Professor Olu Osinowo Signature & Date..... 7/09/15

DECLARATION BY INVESTIGATOR(S)

Protocol number:

To be completed in duplicate, and one copy returned to the Secretary, Research and Ethics Committee, Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State

I/we fully understand the conditions under which I am/we are authorised to conduct the above-mentioned research and I/we guarantee that I/we will ensure compliance with these conditions. Should any departure be contemplated from the research procedure as approved, I/we undertake to resubmit the protocol to the Research and Ethics Committee.

Signature ..... Date..... 14/09/2015

DELTA STATE UNIVERSITY TEACHING HOSPITAL
P.M.B. 07 OGHARA, DELTA STATE, NIGERIA

HEALTH RESEARCH ETHICS COMMITTEE
C/O Department of Obstetrics & Gynaecology
E-mail: hrecdelsuth@gmail.com
Phone No +2340837560538

31/08/2015

Our Ref: DELSUTH/HREC/2015/024

Dr. Abimbola Olowofela

Madam,

LETTER OF ETHICAL APPROVAL FOR RESEARCH STUDY

Your proposed research study titled: **"Evaluation of Pharmacovigilance Systems Performance in South – South Nigeria"** was considered in the Health Research Ethics Committee meeting held on the 27th August 2015. An approval has been granted.

You are therefore requested to carry out the research in accordance with the approved protocol and submit progress report of the research every 6 month.

The duration of the approval is one year. After this period, you are required to re-apply for renewal, if the research work is yet to be completed.

Thank you.

Dr. P. I. Okonta
Chairman

Dr. Abadom E. G
Secretary

UNIVERSITY OF UYO TEACHING HOSPITAL

P.M.B. 1136, UYO, AKWA IBOM STATE

e-mail: info@uuthuyo.com; uuthuyo@gmail.com

Prof Etete J. Peters, FWACP, FCCP, Cert Pulm (Tel Aviv)
CHIEF MEDICAL DIRECTOR

Mr. Biyi Otegbeye, B.Sc., MBA, ACIS, LLB, BL
CHAIRMAN, BOARD OF MANAGEMENT

Mr.Thompson T. Ikpe B.Sc., M.Sc., MNIM, ACIPM
DIRECTOR OF ADMINISTRATION

Our Ref: UUTH/AD/S/96/VOL.XIV/357

Your Ref: _____

Date: November 13, 2015

UNIVERSITY OF UYO TEACHING HOSPITAL, UYO INSTITUTIONAL HEALTH RESEARCH ETHICAL COMMITTEE (IHREC)

APPROVAL CERTIFICATE LETTER

Principal Investigator: **Dr. Abimbola Olowofela**

Protocol Title: **"EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH NIGERIA"**

STATUS

The University of Uyo Teaching Hospital, Uyo Institutional Review Committee has reviewed your protocol title: **"EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH NIGERIA"**

The research protocol described above has been approved by the University of Uyo Teaching Hospital, Uyo Institutional Health Research Ethical Committee (IHREC) as indicated.

J. E. Inyang
Secretary, UUTH
Uyo IHREC

UNIVERSITY OF PORT HARCOURT TEACHING HOSPITAL

P.M.B. 6173. PORT HARCOURT - website: www. upthnigeria.org

CHAIRMAN
DR. SEGUN OGUNDIMU
MBBS (Lagos) FWACP, FACPE

DIRECTOR OF ADMINISTRATION
B. AMAOMU-JUMBO (MRS.)
M.Sc. (UK) MCMI (UK) MNIM (CHARTERED) FHAN, FWIMA

CHIEF MEDICAL DIRECTOR
PROF. AARON C. OJULE, JP
MBBS, M.sc, FMCPath. FNIM, FHAN

CHAIRMAN, MEDICAL ADVISORY COMMITTEE
DR. CHARLES I. TOBIN-WEST
MD, MPH, FMCPH, Adv Dip Admin.

HOSPITAL ETHICAL COMMITTEE

UPTH/ADM/90/S.II/VOL.X/668 29th June 2015

Dr. A. Olowofela
Department of Medicine
School of Medicine
College of Medical Sciences
University of Benin
Benin City

ETHICAL APPROVAL

EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH, NIGERIA

We refer to your letter dated 8th June 2015 requesting for Ethical Approval of your research project titled "**Evaluation of Pharmacovigilance System Performance in South-South, Nigeria**".

After a critical appraisal of your proposal by the University of Port Harcourt Teaching Hospital Ethical Committee and the Research Ethics Group of the Centre for Medical Research and Training, College of Health Sciences, University of Port Harcourt, approval is hereby given to you to commence your study.

Note the following:

1. The study can only be started after it is approved by the examining body.

The Hospital reserves the right to withdraw this approval if at any time during the conduct of the study you infringe on the ethical regulations of the Hospital or the ethical rights of your study subject.

B. J. Thom-Manuel (Mrs.)
Secretary
for: Chairman

HEALTH RESEARCH ETHICS COMMITTEE
UNIVERSITY OF CALABAR TEACHING HOSPITAL

P. M. B. 1278, CALABAR, NIGERIA

Our Ref:_____

Your Ref:_____

Date: 27TH AUGUST, 2015

NOTICE OF FULL APPROVAL OF PROTOCOL
EVALUATION OF PHARMACOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH NIGERIA

UCTH HEALTH RESEARCH ETHICS COMMITTEE REG. NUMBER:	**NHREC/07/10/2012**
Health Research Ethics Committee Protocol Assigned Number:	**UCTH/HREC/33/360**
Name of Principal Investigator:	**ABIMBOLA OLOWOFELA**
Address of Principal Investigator	**DEPARTMENT OF MEDICINE UNIVERSITY OF BENIN TEACHING HOSPITAL, BENIN CITY**
Date of Receipt of Valid Application:	**8TH JUNE, 2015**
Date of Meeting where determination of Research was made:	**14TH AUGUST, 2015**

This is to inform you that the Research described in the submitted protocol, the Consent Forms, and other participant information materials have been reviewed and given *full approval by the Health Research Ethics Committee.* This approval dates from 14th August, 2015 to 13th July, 2016. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. In multi year research, endeavour to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserves the right to conduct compliance visit to your research site without previous notification.

Prof. Martin Meremikwu
CHAIRMAN, UCTH HREC

UNIVERSITY OF BENIN TEACHING HOSPITAL
P.M.B. 1111 BENIN CITYNIGERIA

Telephone: 052-600418
Telegram: UNITECHOS, BENIN
Telex: 41120 NG
Website: ubth.org

CHAIRMAN: GEN. A.B. MAMMAN (RTD)
mni, FSS, psc, OFR
E-mail: ashehg2@yahoo.com;
genabmammanalshahi@yahoo.com

CHIEF MEDICAL DIRECTOR: PROF.M.O. IBADIN
MBBS (Benin), FMCP, (Paed) M.S. (IMMUNOLOGY & IMMUNOCHEM)
E-mail:mikobadin@yahoo.com;
mikobadin@ubth.org

CHAIRMAN, MEDICL ADVISORY COMMITTEE: PROF. G.E. OFOVWE
B.M, B.ch, FWACP (Paed
E-mail: ofovwegabriel@gmial.com

DIRECTOR OF ADMINISTRATION: A.P. OMOREGIE (MRS)
B.Sc, MSc, MHPH
E-mail: officeoftheda@ubth.org

ETHICS AND RESEARCH COMMITTEE CLEARANCE CERTIFICATE

PROTOCOL NUMBER: ADM/E 22/A/VOL. VII/1245

PROJECT TITLE: "EVALUATION OF PHARMCOVIGILANCE SYSTEM PERFORMANCE IN SOUTH-SOUTH NIGERIA"

PRINCIPAL INVESTIGATOR(S) DR. ABIMBOLA OLOWOFELA

DEPARTMENT/INSTITUTION: CLINICAL PHARMACOLOGY AND THERAPEUTICS UNIT, UNIVERSITY OF BENIN/UNIVERSITY OF BENIN TEACHING HOSPITAL, BENIN CITY, NIGERIA

DATE CONSIDERED AUGUST 17TH, 2015

SUPERVISOR(S): PROF. AMBROSE O. ISAH, PROF. ANNIE FOURRIER

DECLARATION DECISION OF THE COMMITTEE: APPROVED

REMARK:

CHAIRMAN: PROF. A.N. ONUNU **SIGNATURE & DATE**..... 17/8/2015

DECLARATION BY INVESTIGATOR(S):

PROTOCOL NUMBER (please quote in all enquiries)

To be completed in four and three copies returned to the secretary, Ethics and Research committee, Clinical services and Training Division, University of Benin Teaching Hospital Benin City.

I/We fully understand the conditions under which I am/we are authorized to conduct the above mentioned research and I/We undertake to resubmit the protocol to the Ethics and Research Committee.

Signature..... **Date**...01.09.2015.....

Appendix III: Slides of educational seminar

Pharmacovigilance in South-South Nigeria

Abimbola Olowofela.
MBBS, FWACP,FMCP
Consultant Physician/ Clinical Pharmacologist
South-South Zonal Pharmacovigilance Centre
University of Benin Teaching Hospital
Benin-City, Nigeria

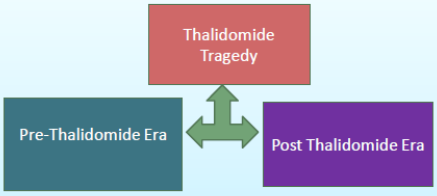
Outline

- Introduction
- Historical Perspective
- What is Pharmacovigilance
- Why do we need Pharmacovigilance
- Structure of Pharmacovigilance in Nigeria
- Achievements of Pharmacovigilance in Nigeria
- Adverse Drug Reaction reporting- types, procedures and importance of reporting.
- Benefits of reporting and FAQs..
- Conclusion.

- Cur'd yesterday of my disease
- I died last night of my physician.

- *The remedy worse than the disease.*
  – *Matthew Prior (1664-1721).*

Historical Perspective



Pre Thalidomide Era

- 1848- Anaesthesia induced death, Lancet set up inquiry to collect case reports on similar cases.
- 1906- US FDA- passes law to ensure drugs are pure and free from contamination.
- 1937- 107 deaths in US from diethylene glycol poisoning mixed with sulfanilamide.

Historical perspective

- The international monitoring of drugs came into limelight in the 1960s following the thalidomide incident
- Pregnant women took a hypno-sedative drug to ameliorate morning sickness, which would later cause an abnormality in the new born.
- This abnormality was the first evidence discovered by a gynaecologist who noticed the birth defects in the new born and traced it to the medicines used in pregnancy
- This sparked off an inquiry into drug use worldwide.

Pharmacovigilance in Nigeria- History

1989- Poorly compounded Chloroquine kills several children in Enugu

1990- Diethylene glycol disaster in Jos & Ibadan killing 109 children

1994-Creation of a Drug & Poison Information Centre in UBTH

2002-2004- Contaminated infusions discovered. Substandard Epinephrine used during Open heart surgery

2004- Nigeria National Pharmacovigilance Centre (NAFDAC) joins WHO-International Drug Monitoring Program

2005- National Drug Policy- emphasises Drug SAFETY and pharmacovigilance

2013- National Pharmacovigilance Policy was adopted

2013- Creation of Zonal Pharmacovigilance Centres

Definition of Pharmacovigilance

- Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems.

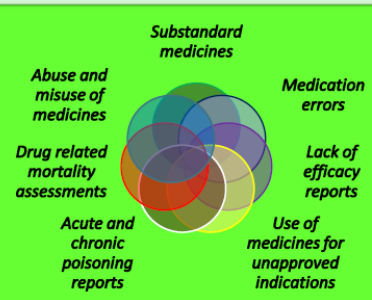
Product concerns in Pharmacovigilance

- Herbal medicine
- Traditional and complementary medicines
- Blood products
- Biological
- Medical devices
- Vaccines

Products Concerns

13

Scope of pharmacovigilance



Why pharmacovigilance

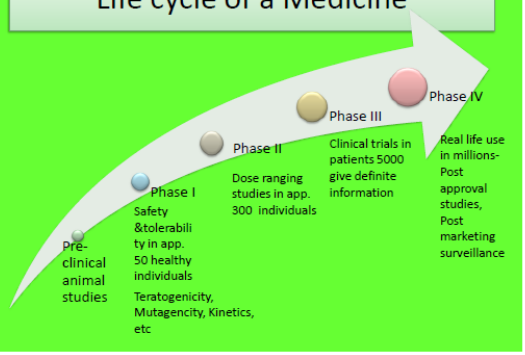
- Improve patient care and safety relating to medicine use.
- Improve public health and safety in relation to use of medicines.
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging safe, rational and a cost effective use.
- Promote understanding education and training in pharmacovigilance with effective communication to the public.

WHO Importance of Pharmacovigilance, 2002

Why Pharmacovigilance

- Animal testing is not sufficiently indicative of safety in humans.
- Numbers in clinical trials are few and the conditions of use differ from the clinical practice.
- Incomplete or unavailable information about rare reactions, Non-inclusion of special population such as elderly patients, children and pregnant women.
- Ethnic, regional, geographical Dietary differences worldwide.

Life cycle of a Medicine

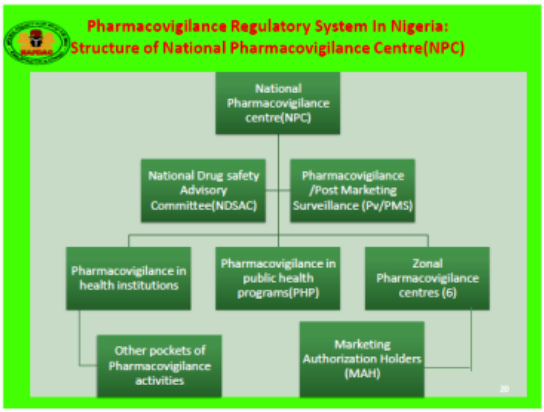


Methods of Pharmacovigilance

- **Evaluation of the Phase I/II/III trial reports** for dose-response ,safety and tolerability of new therapeutic agents .
- **Post Marketing monitoring systems**
  - Spontaneous reports:
  - Prescription event monitoring
  - Record linkage studies
  - Case control studies
  - Mandatory reports

Methods

- Spontaneous reports: A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the National Pharmacovigilance Centre.
  - Most common form of reporting ADRs.
- Mandatory Reporting: carried out by the market authorisation holders
  - Reported back to the National Pharmacovigilance Centre as a Periodic Safety Update Report.



Legal basis for pharmacovigilance

- The National Agency for Food and Drug Administration and Control (NAFDAC)Decree 15 of 1993 amended to Act CapN1 law of the Federal Republic of Nigeria 2004.
  - "To control and regulate the manufacture, importation, exportation, distribution, advertisement, sale and use of food , drugs, cosmetics, chemicals/detergents, medical devices and all drinks including packaged water"
- NAFDAC ensures **safety,** quality, efficacy, and rational use of all the aforementioned.

Pharmacovigilance in Nigeria

- Establishment of the National Pharmacovigilance Centre in Abuja, Nigeria
- Training of health care workers on pharmacovigilance.
- Increasing number of reports in the database.
- Increasing use of electronic media to publicise pharmacovigilance.
- Creation of Zonal Centres in 2013. UBTH Benin-City is the Zonal pharmacovigilance Centre for South -South Zone
- Stand-alone pharmacovigilance policy document.

Some Regulatory decisions taken as a result of pharmacovigilance activities

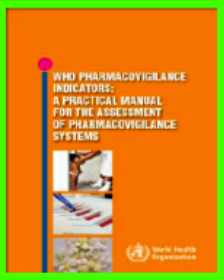
s/n	Drug	Reasons for action taken	Regulatory decision taken	Year action was taken
1	Tramadol	Irrational Use & Increased Reports of ADRs	Process of Reclassification of Drug From POM to Controlled Drug ongoing	2012
2	Infusions	Contaminated infusion	Mop up of affected batches, manufacturer's GMP re-evaluated, intervention in storage facility of HCPs	2011
3	Rosiglitazone	Risk of congestive heart failure	NRA Directed MAH to voluntarily withdraw product from circulation in Nigeria	2011
4	Codeine Containing Cough syrups	Wide spread abuse of drug	Drug abuse campaign, reduction of quantities approved for manufacturing,	2011
5	Gentamicin 280mg/2ml	Increased risk of ototoxicity and nephrotoxicity and increased risk of endotoxin reactions	Recall/mop of gentamicin 280/2ml from circulation	2010
6	Teething mixture	Low benefit/risk ratio	Banned in Nigeria	2009

Pharmacovigilance in Nigeria- Limitations

- Underreporting of ADR by the public, healthcare workers.
- Socio –cultural belief about health and practices.
- Inadequate funding of pharmacovigilance.
- Inadequate staffing to handles various aspects of pharmacovigilance.
- Fear of litigation.
- Hesitation in reporting.

Assessment of Pharmacovigilance

- WHO indicators
  - Structures
  - Processes
  - Outcomes
- Determining functionality of pharmacovigilance at the institutional level.



What is an Adverse Drug Reaction....

- Adverse Reaction - A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Definitions: Serious Adverse Drug Reaction

- A serious Adverse Reaction - any untoward medical occurrence that at any dose:
  - results in death
  - is life threatening
  - requires patient hospitalization or prolongation of existing hospitalization
  - results in persistent or significant disability/incapacity
  - causes a congenital anomaly or birth defect
  - requires an intervention to prevent permanent impairment or damage.

ADR definitions

- **Adverse Event/Adverse Experience - Any untoward medical occurrence that may** appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

Definition

- **Side effect** - Any unintended effect of a pharmaceutical product occurring at a dose normally used in man, which is related to the pharmacological properties of the drug.
- **Unexpected Adverse Reaction** - An adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug.

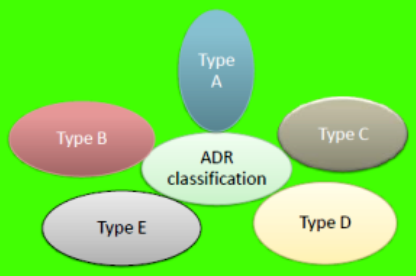
Epidemiology of Adverse Drug Reactions

- Adverse drug reactions are ranked about the 4th to the 6th leading causes of death in the industrialised world.
- The economic burden of adverse drug reaction worldwide is enormous resulting in billions of dollars spent on drug related events.

Epidemiology of adverse drug reactions

- The quantification of the economic burden has not been properly elucidated and is likely to be unknown.
- However, judging by the pattern of drug use in Nigeria, it is very likely that the burden may be enormous.

Classification of ADR



Types of adverse drug reactions

- **Type A Reactions 'augmented'** reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent.
  - Examples include respiratory depression with opioids or bleeding with warfarin.

Types of adverse drug reactions

- **Type B Reactions or 'bizarre'** reactions are aberrant responses that are not expected from the known pharmacological actions of the drug when given in usual therapeutic dose
  - Examples include anaphylaxis with penicillin or skin rashes with antibiotics

Types of adverse drug reactions

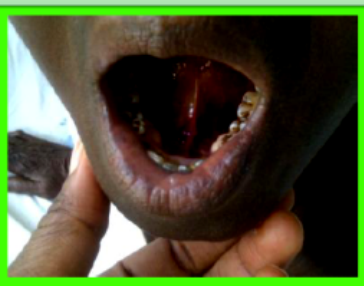
- **Type C Reactions** or **'continuing'** reactions, persist for a relatively long time.
  - An example is osteonecrosis of the jaw with bisphosphonates, analgesic nephropathy
- **Type D Reactions or 'delayed'** reactions, become apparent some time after the use of a medicine. The timing of these may make them more difficult to detect.
  - Retinoid associated teratogenesis.

Types of adverse drug reactions

- **Type E Reactions** or **'end-of-use'** reactions, are associated with the withdrawal of a medicine.
  - An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines

Steven Johnson Syndrome following co-trimoxazole

Warfarin induced bleeding



Reports in the database

Figure 1: INDIVIDUAL CASE SAFETY REPORTS RECIVED AT THE NPC, NAFDAC FROM SEPT 2004 TO MAY 2015.

Reports in the database

Fig 2: SYSTEM ORGAN CLASSIFICATION OF REPORTED ADRs (WHO MedDRA) in the NAFDAC database from September 2004 till August 2015.

Reports in the database

Fig 3: Pharmacological classification of reported ADRs (WHO-DD)

Challenges of ADR reporting

- Different medicines may cause the same clinical scenario.
- A particular medicine may be responsible for different clinical syndromes and disease pattern.
- Geographical and ethnic differences may alter the adverse reaction profile.
- Causality may be difficult in different patients.
- Aetiology, frequency and pathology of many complaints and disorders are still uncertain.

Evans SA. Causation and Diseases: the Henle-Koch postulates revisited. Yale J Biol Med 1976; 49: 175-95

Factors contributing to ADRs

- Inadequate knowledge of Pharmacology – especially adverse effects of drugs
- Irrational use of drugs and poor prescribing patterns
- Promotional activities by pharmaceutical company detailers
- Lack of objective sources of information
- Liberal drug outlets and unhealthy pharmaceutical practices
- Liberal OTC and self medication practices
- "Drug gifts" from overseas
- Ignorant, illiterate public

Isah A.O. Pharmacovigilance

Factors contributing to ADRs

- Patient factors
  - Age
  - Sex
  - Genetic abnormalities
  - Previous adverse drug reactions
  - Presence of organ dysfunction
  - Co-morbid states
  - Race and ethnicity
- Health care worker factors
  - Incorrect medicine or combination
  - Incorrect route
  - Incorrect dose
  - Wrong duration of therapy
  - Drug dose and duration of therapy
  - Poor dispensing practices
  - Inadequate counselling.

Factors contributing to ADR

- **Pharmaceutical factors**
  - Parent compound
  - Metabolite
  - Excipient
  - Drug delivery systems
  - Drug-drug interactions
  - Dispensing errors

Recognising ADR/ Drug Related Problem

- Largely unrecognised and under-reported.
- Evaluate reasons for discontinuations/ dosage reductions of medicines.
- Screen all medications
- Investigate abnormal laboratory results in context of present medications.
- Regular chart reviews.

Preventing Adverse drug reactions

- High index of suspicion
- Know your patients' drugs [incl. OTC drugs and herbal remedies]
- Avoid unnecessary medications
- Recognize high risk patients.
- Make informed choices/Keep drug interactions in mind.
- Monitor patients carefully
- Educate your patients
- Stay informed about medicines

Goldman et al 1999

What Next?

- Document and report ALL suspected adverse drug events especially in patients' case record.
- Stop Medicine and try to identify the suspected Drug.
- Fill out a yellow ADR form with the essential components.
- Send out form to local pharmacovigilance centre, NAFDAC or to the Zonal Pharmacovigilance Center in UBTH for onward transmission.
- NO PUNITIVE MEASURES FOR REPORTING!!!

What to report on

- Adverse drug reaction
- Serious adverse drug reactions
  - Orthodox medicines
  - Biological medicines including vaccines
  - X-ray contrast media
  - Consumable Medical products
  - Cosmetics
  - Traditional and herbal remedies, etc
- Medication errors
- Therapeutic ineffectiveness
-

What to report

- Adverse drug reactions
- Therapeutic ineffectiveness
- Cases of drug misuse and abuse
- Cases of acute and chronic poisoning
- Overdose
- Medication Errors
- Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medicinal products

When Do I Report?

Who can report

- Health workers-
  - Doctors,
  - Nurses,
  - Pharmacists
- Patients
- Pharmaceutical companies
- Patent Medicine Stores,
- Traditional medicine clinics
- Nursing homes

How to report

- Use an adverse drug reaction reporting form(next slide)
- You can pick up form from the Local Pharmacovigilance centre- the OPD pharmacy/ at the wards / clinics here in UCTH or
- You can download form from the NAFDAC website. www.nafdac.org
- Send form to the local pharmacovigilance committee- (Headed by Prof Udofia) located at the OPD pharmacy here in UCTH.
- Also Scan and email report to the Zonal Pharmacovigilance Centre UBTH at zpcsouthsouth@gmail.com or call the ZPC on 09092474258

How to report

Health care providers can also obtain ADR reporting forms or send completed forms using any of the following channels:

- The National Pharmacovigilance Centre (NPC) – NAFDAC
  Plot 2032 Olusegun Obansanjo Way
  Wuse Zone 7, Abuja.
- NAFDAC offices in the 36 states & FCT
  - Reports can also be scanned & emailed to npcadr@nafdac.gov.ng, npc_nafdac@yahoo.com
- By Telephone: 08086899571 or 07098211221
- Zonal Pharmacovigilance Centres

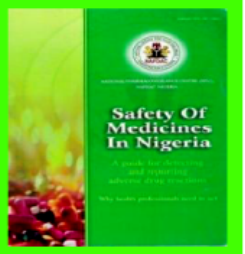
Local Pharmacovigilance Centre

- OPD pharmacy- Drug Information Centre
- Pharmacist available to handle drug information
- Forms are available during working hours.
- Dedicated phone line soon to be available at the centre
- Dedicated bucket files to house YELLOW FORMS will be made available soon in the wards and clinics.
- Access yellow forms from ALL hospital pharmacy outlets.

Zonal Pharmacovigilance Centres - Focal persons

s/n	Head of ZPC	Institution	Email	Phone. no
1.	Dr. Abimbola Olowofela	UBTH	felabimbola@yahoo.com	08037075435
2.	Dr. Frank Omoha	FMC,Owerri	ugofrankp@yahoo.com	08033471803
3.	Dr. A. Adweunmi	LUTH	debojibs@yahoo.com	08069433629
4.	Pharm. Susan Ayetoro	UITH	Susanayetoro@yahoo.com	08033028703
5.	Pharm. Foluke Garnett	ABUTH	folugarnett@yahoo.com	08033018813
6.	Dr. Mohammed Talle	UMTH	abdultalle@yahoo.com	08028256040 08172505145

Nigeria ADR form and Guide Booklet

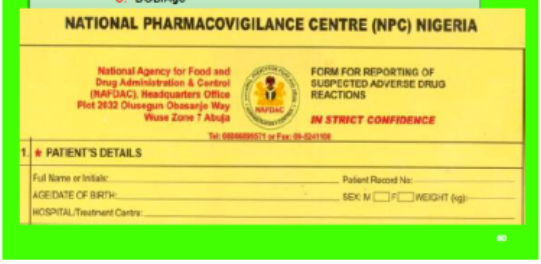


Essential components of ADR yellow form

- Patient demographics
- Suspected product's name and manufacturer
- Relevant history and pre-existing medical conditions
- Other medications or treatments
- Detailed description of the adverse event and its management
  - Date of onset and date reaction ended or if ongoing
  - Dates and times that suspected drug was started and stopped
  - Dose, frequency, and route/method of drug administration
- Outcome of event (e.g., death, disability, prolonged hospitalization)
- Relevant laboratory tests or diagnostic findings
- Information regarding dechallenge
- Presence of confounding variables

Tools used in spontaneous reporting
Minimum Reporting Requirement

1. An identifiable patient-
   A. Name/Initials
   B. Sex
   C. DOB/Age



NATIONAL PHARMACOVIGILANCE CENTRE (NPC) NIGERIA

National Agency for Food and Drug Administration & Control (NAFDAC), Headquarters Office Plot 2632 Olusegun Obasanjo Way Wuse Zone 7 Abuja

FORM FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS

IN STRICT CONFIDENCE

1. ★ PATIENT'S DETAILS

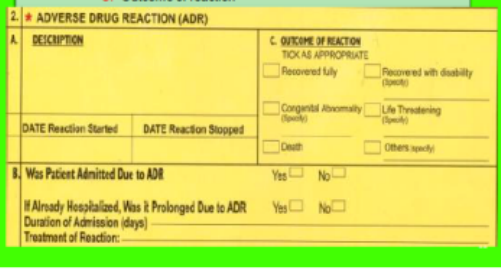
Full Name or Initials: Patient Record No:

AGE/DATE OF BIRTH: SEX: M F WEIGHT (kg):

HOSPITAL/Treatment Centre:

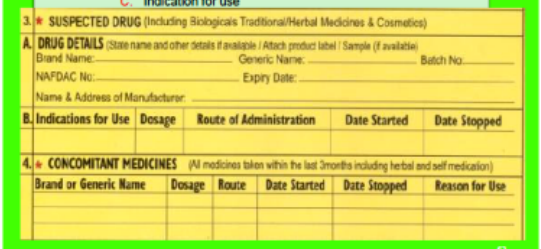
Tools used in spontaneous reporting
Minimum Reporting Requirement

2. Description/Dates of the suspected reaction-
   - A. Brief description of the reaction
   - B. Date ADR started and stopped
   - C. Outcome of reaction



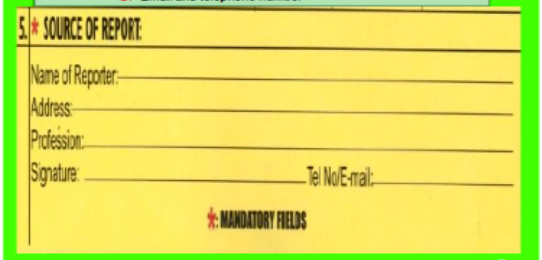
Tools used in spontaneous reporting
Minimum Reporting Requirement

3 & 4. Name of suspected product-
   - A. Name of drug
   - B. Date started and stopped
   - C. Indication for use



TOOLS USED IN SPONTANEOUS REPORTING
Minimum Reporting Requirement.

5. An identifiable source of Information/Reporter-
   - A. Name of reporter
   - B. Email and telephone number



Why people don't report

- Insufficient information
- Difficulty in determining if an ADR has occurred.
- Not certain if the case should be reported.
- A single report may not make a difference.
- I should receive some incentive for reporting
- It takes too much time to report
- Reporting does not put your career at risk

Herdeiro MT- Improving adverse reaction reporting in Portuguese professionals- Thesis 2005.

FAQs in pharmacovigilance

- **What happens to my report**
  - It is sent to the zonal centre for onward transmission to the national centre and then forwarded to the WHO international database.
  - May lead to regulatory actions such as withdrawals, banned medicines,
  - Improves drug safety in Nigeria.
  - A feedback is sent to the reporter either via email or phone call.
- **Is there any risk to reporting**
  - No- there is no risk, because punitive actions are not taken from reporting ADRs.
- ADR reports cannot be used in a court of law

Routes of improving ADR reports

- Easy access to ADR forms
- Feedback to reporters
- Facilitate reporting-(via computers)
- Publish ADR reports in scientific journals
- Include ADR reporting in student curricula

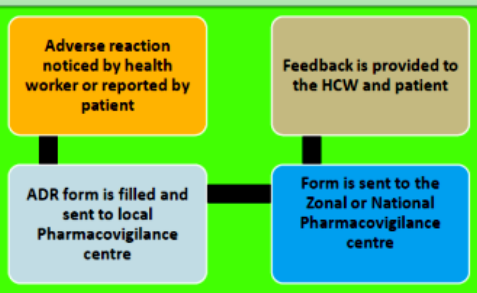
Benefits of reporting

- Improves safety of medicines
- Improves quality of care of patients.
- Increases patient confidence in health care practitioner.
- Contribute to global safety on use of medicines.

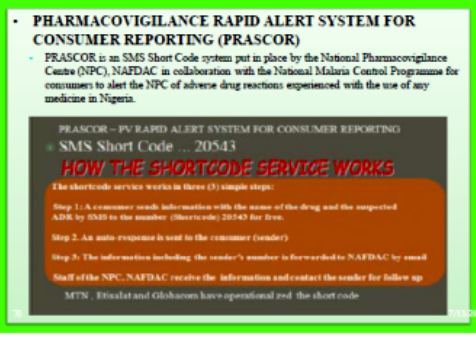
Responsibilities of The HCW

- Ensuring rational prescribing, dispensing and administering of medicines to patients
- Detecting and reporting ADRs and other medicine related problems occurring in patients
- Educating patients on rational use of medicines.
- Educating and counseling patients on the need to report ADRs and other medicine related problems when they occur.
- Educating other healthcare providers on PV and rational use of medicines

Algorithm of reporting



Consumer reporting - PRASCOR



Conclusion

- The success or failure of any spontaneous reporting system depends on the active participation of reporters.
- Collective participation by all stakeholders in pharmacovigilance is essential to improving patient safety.

Acknowledgements

- The management and staff of UCTH
- Prof. A.O. Isah
  - Pharmacovigilance presented at the Nigerian PG update course Lagos, 2011.
- National Pharmacovigilance Centre (NPC) NAFDAC
  - Pharmacovigilance Training materials
- Dr. S.A. Ayinbuomwan. Clinical Pharmacology Unit, UBTH.

THANKS FOR LISTENING

Chapter 8 PhD portfolio

Name: Abimbola O. Opadeyi (Formerly *Abimbola Olowofela*)

PhD Training -Eu2P courses (www.eu2p.org)

Medicines Pharmacovigilance and regulatory aspects (3 ECTS, grade B)
Drug utilisation: qualitative methods (3 ECTS, grade B):

Conference participation

- Facilitated at a 3 day training of senior health professionals in the Delta State Ministry of Health on basic and intermediate pharmacovigilance principles from 2nd to 4th July, 2014 Asaba, Delta State, Nigeria.

- Co-organised with NAFDAC and also facilitated at a Zonal sensitization workshop/training on rational use of medicines and pharmacovigilance on January 27th 2015 for selected healthcare professionals in Edo and Delta State.

- 17th World Congress of Basic and Clinical Pharmacology (WCP2014) July 2014. "Medication use practices in a tertiary health care hypertension clinic in Nigeria by **Olowofela A** and Isah A.O"

- Annual General and Scientific Meeting of the West African College of Physicians, Nigerian Chapter- Owerri. 2015.

- 2nd African Society of Pharmacovigilance Meeting. Accra, Ghana. November, 2015

- Training of Trainers workshop by the West African College of Physicians, 2016.

- Nigerian Hypertension Society Annual General Meeting and Scientific Conference 2016.

- Annual General and Scientific Meeting of the West African College of Physicians, Nigerian Chapter- Asaba 2017.

Teaching experience at higher-education level

Teach medical and dental students as well as internal medicine residents' formal lectures, seminars and bedside teaching. March 2012 till date,
Therapeutic teaching rounds to four hundred level and final year medical students.
Presentation at clinical meetings to internal medicine trainees and final year medical students of the University of Benin, March 2012 till date

Publications

1. **Olowofela, A**., Fourrier-Reglat, A., Isah, A.O., (2016) Pharmacovigilance in Nigeria: an Overview. ***Pharmaceutical Medicine; 2016; 30(2): 87-94.***
2. **Opadeyi, A**., Fourrier-Reglat, A., Isah, A.O., Assessment of the state of Pharmacovigilance in the South-South Zone of Nigeria using WHO Pharmacovigilance indicators. ***BMC Pharmacology and Toxicology. 2018;19: 27.***

3. **Opadeyi, AO**., Fourrier-Reglat, A., Isah, A.O., Drug utilisation pattern in South- South Nigeria using the WHO Core drug prescribing indicators. Submitted to Tropical Medicine and International Health. October 26th 2018
4. **Opadeyi, AO**., Fourrier-Reglat, A., Isah, A.O., Knowledge, Attitude and Practice of health professionals regarding Pharmacovigilance in South-South Nigeria. Submitted to Pharmacoepidemiology and Drug Safety.April 18th 2018
5. **Opadeyi, AO**., Fourrier-Reglat, A., Isah, A.O., Educational intervention to improve the knowledge, attitude and practice of Health Care Professionals regarding pharmacovigilance in South-South Nigeria. Submitted to Therapeutic Advances in Drug Safety May 30th 2018
6. **Opadeyi, AO**., Fourrier-Reglat, A., Isah, A.O., Impact of an educational intervention on adverse drug reaction reporting in tertiary hospitals in South-South Nigeria. Submitted to Expert Opinion on Drug Safety. October 26th 2018
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9. **Olowofela A.,** and Isah, A.O. A Profile of Adverse Effects of Antihypertensive Medicines in a Tertiary Care Clinic in Nigeria***. Annals of African Medicine. 2017; 16(3): 114-119.***
10. **Olowofela, A.,** Ayinbuomwan, S.A. Isah, A.O. Sources of information on the use of medicines utilized by resident doctors in a tertiary health care facility in Nigeria. ***Highland Medical Research Journal. 2017;17(2):81-85.***
11. **Olowofela, A.,** Ayinbuomwan, S.A., Isah, A.O. The internet as a source of drug information: A profile of utilization by junior hospital doctors in a Nigerian teaching hospital. ***Annals of Biomedical Science. 2017; 16(2): 226-233.***
12. **Olowofela, A.**, and Isah, A.O., Dietary habits of hypertensive patients in a tertiary hypertension clinic in southern Nigeria. ***Journal of Medicine and Biomedical Research. 2016;15(2):23-33***
13. **Olowofela, A.**, and Isah, A.O. Antihypertensive medicines prescriptions before and after the Nigeria Hypertension Society guidelines and prescriber's awareness of the guideline. ***Nigerian Medical Journal. 2017;58(3):107-113***
14. Ayinbuomwan SA, **Opadeyi A**, Isah AO**.** Management of snakebite victims using low dose antisnake venom in a tertiary hospital in Southern Nigeria: A 5-year retrospective study. **Research Journal of Health Sciences**. 2018; 6(2): 82-89.
15. **Olowofela A** and Isah AO. Medication use practices and inspection of returned pills during follow up attendance at a tertiary care hypertension clinic in Nigeria. ***Sahel Medical Journal*** *2018, 21: 128-36*