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Pharmacovigilance core indicators practices in some health facilities in Osun state, Nigeria

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ABSTRACT

Background: World Health Organization pharmacovigilance core indicators have been recommended as a useful tool towards improving pharmacovigilance activities. Following the limited information on adverse reactions reporting in some institutions, the study assessed the status of pharmacovigilance in tertiary and secondary hospital facilities in Osun State, Nigeria with a view towards improving the pharmacovigilance system.
Methods: A cross-sectional descriptive survey was conducted in the two tertiary hospitals and eight state hospitals in Osun State. The data was assessed using modified WHO core pharmacovigilance indicators.
Results: Characteristics of the health facilities included the number of hospital beds; Tertiary 920(70.67%), Secondary 346(29.33%); Hospital workers, Doctors 1044(41.45%), Nurses 1395(55.38%), Pharmacists 80(3.18%) and Number of Out-patients 300915(95.49%)/ In-patients 14199(4.51%). All facilities had a pharmacovigilance focal person responsible for pharmacovigilance activities. None of the facilities had a financial provision for pharmacovigilance activities. All the centers had standard adverse drug reactions reporting form. On Core Processing Indicators (CPI) the absolute value of ADR reports received in ten hospitals in the previous year ranged from 0 to 17. The total reports in the local database ranged from 2 to 76. There were no adequate data to assess other parameters in the center. On Core Outcome/Impact Indicators (CO/II), the number of medicine-related hospital admissions per 1000 admissions ranged from 0.45 to 2.02 and there were no documentations from medical records/registers in the various hospitals of medicine related deaths. Information on other pertinent data was inadequate in making computation of other outcome indicators in the health facilities.
Conclusion: Pharmacovigilance activities were observed to be lacking in most of the health facilities. Factors such as poor funding, lack of documentation were prominent. It is therefore recommended that concerted effort should be made to strengthen the practice in all units of healthcare delivery.

1. Introduction

The history of pharmacovigilance started with the thalidomide disaster in the 1960s which led to congenital deformity (Phocomelia) in neonates born to mothers who used thalidomide to treat morning sickness during pregnancy[1]. After this disaster, the WHO called for closer monitoring of the adverse effects of all drugs by all countries[2]. Also, sulfanilamide tragedy of 1937-Diethyl glycol toxic ingredient used caused death of more than 100 people in the United States. In February 2009, about 84 Nigerian children died after taking a medicine called "*My Pikin Baby Teething Mixture*", a syrup for treating teething pain and pyrexia according as recommended by the manufacturer. Investigation by the National Agency for Food Drug Administration and Control (NAFDAC) traced the death again to the use of diethylene glycol, as an excipient that causes kidney and liver damage as well as attacking the central nervous system; thus causing paralysis

that hampers breathing[3]. Early in the month of October 2019, NAFDAC in Nigeria just like other regulatory counterparts in the globe, issued a public alert on genotoxic impurity N-Nitrosodimethylamine (N-NDMA) in branded Zantac® (Ranitidine injection 50mg /mL; batch no 669). The N-NDMA has been classified by International Agency for Research on cancer (IARC) as probably carcinogenic[4]. Although, the occurrence of some of these reactions may not be predictable but sufficient knowledge of the conditions under which they are likely to occur may prevent their occurrence. The WHO initiated an international program for monitoring the safety of medicines in 1978, which is coordinated by Uppsala Monitoring Centre Sweden and had 136 full members and 30 associate members as at 4th June 2019. This program is known as pharmacovigilance[5]. Pharmacovigilance Indicators has been classified[6] and recommended. The need for adoption in most health facilities has also been buttressed[7]. Health facilities as in Osun State need to be assessed because of the enormous services they render to the large populace. The study therefore assess the status of pharmacovigilance activities using the WHO recommended indicators in Osun State secondary and secondary health facilities.

2. Method

The study was carried out in Osun state Nigeria as one of the key states in the south-west Nigeria with a population of over 3.42 million[8], and nine Zonal State Hospital and a State owned and one Federal Government owned tertiary hospital. The state had 30 local government, 3 senatorial districts and one area office recognized by the Federal government of Nigeria. The health care professional in all tiers of hospital in the state could send their reports either directly or through the zonal Pharmacovigilance center for onward delivery to the national pharmacovigilance center in Abuja Nigeria. In Nigeria, health care is delivered at three levels; primary, secondary and tertiary. Tertiary care hospital provides the highest level of care and serves as referral centers for the primary and secondary centers. Two categories of hospitals (Nine secondary and three tertiary hospitals) were selected for the study because they provide the good coverage of services, fair accessibility and they have wide range of healthcare workers. Prior to the study, ethical approval with number OSHREC/PRS/569T/157 was obtained from the ministry of health Osun state. The selected centers were Ladoke Akintola University Teaching Hospital (LAUTECH) Osogbo; State Specialist Hospital, Ila–Orangun; State Specialist Hospital, Iwo; State Specialist Hospital, Ikire State Specialist Hospital, Ikirun State Specialist Hospital, Ipetu – Ijesa, State Specialist Hospital Ilesa; State Specialist Hospital Ede; State Specialist Hospital Ile – Ife, Obafemi Awolowo University Teaching Hospital (OAUTHC) Ile Ife. The data were gathered using a modified WHO pharmacovigilance indicator form as recommended and utilized National Pharmacovigilance Centre[9,10]**.** The components of research instrument form included the background information, structural indicators, process indicators and output/ impact indicators. The background information collected wee characteristic of the Hospital: staff strength that is number of port registration health professionals in different categories such as Doctors, Nurses, Pharmacists and other specialists. The structural indicators assessed the degree of pharmacovigilance structures, systems and mechanisms in any of the settings studies. The basic infrastructure needed to enable good pharmacovigilance activities. The enabling environment needed for pharmacovigilance activities. Other assessments were the processes described in the collection, collation, analysis and evaluation of ADR reports. The factors influencing processes were also included. These measures were assessed directly or indirectly. The outcome/impact indicators measured 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 facility for the previous year (to include the disease statistics of admitted and diseased 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 hospitalized was calculated from the adverse drug reaction reports obtained for the previous year. The sampling technique adopted for this study was a purposive sampling method to enable the proper scope of pharmacovigilance activities in the sampled facilities.

2.1 Data Analysis

Data analysis were both qualitative and quantitative. All hospitals assessed in the study were described according to each indicator. The core structural indicators were qualitative indicators with categorical data analyzed descriptively. The presence or absence of the parameter measured was described for each facility. Analysis of the core process and outcome indicators was quantitative indicators reflecting rates of reports and actual numbers.

They were calculated using frequencies and absolute numbers as specified indicators. The data was analyzed with descriptive statistics using Microsoft excel 2007.

3. Results

3.1 Core Structural Indicators:

The assessment questions of the 10 structural indicators for all the 10 facilities revealed that only one had functional accommodation for PV activities equivalent to 10%. Availability of Nigerian Pharmacovigilance Policy in the facilities, presence of facilities Therapeutic Committee, Standard ADR Reporting form in the facility, Process in place for collection, recording and analysis of ADR, incorporation of Pharmacovigilance into orientation program curriculum of newly employed pharmacist and existence of Pharmacovigilance Advisory Committee in the setting. Also, only 20% of the facility had or incorporated pharmacovigilance into the orientation program curriculum of newly employed doctors while others were not introduced to the program. Newsletters /information bulletin (0%) neither were there any financial/budget allocated to the pharmacovigilance center in the various facilities. Provisions were not made for medication error; counterfeit/substandard medicine; therapeutic ineffectiveness and suspected misuse or abuse, dependence on medicine the ADR reporting form. On Core Processing Indicators (CPI) the absolute value of ADR reports received in ten hospitals in the previous year ranged from 0 to 17. The total reports in the local database ranged from 2 to 76. There were no adequate data to assess other parameters in the center. On Core Outcome/Impact Indicators (CO/II), the number of medicine-related hospital admissions per 1000 admissions ranged from 0.45 to 2.02 and there were no documentations from medical records/registers in the various hospitals of medicine related deaths. Information on other pertinent data was inadequate making calculations or computation of other outcome indicators in the health facility difficult.

Table 1. Summary table of demographic characteristics grouped together

Institution Hospital Bed	Number	%
Tertiary	920	(70.67%)
Secondary	346	(29.33%)
Total	**I,266**	**(100%)**
Profession		
Doctors	1044	(41.45%)
Nurses	1395	(55.38%)
Pharmacist	80	(3.18%)
Total	**2519**	**(100%)**
Number of Patients		
Out-patients	300915	(95.49%)
In-patients	14199	(4.51%)
Total	**315114**	**(100%)**

Summary table of demographic characteristics of tertiary and secondary health facilities

Table 2: The demographic characteristics of the facilities at the commencement of the study

FACTORS	OAUT	LAUTE	SH-1	SH-2	SH-3	SH-4	SH-5	SH-6	SH-7	SH-8	TOTAL
NUMBERS OF BEDS	633 (50%)	287 (22.67%)	40 (3.16%)	30 (2.37%)	50(3.95%)	66(5.21%)	50(3.95%)	40 (3.16%)	20 (1.58%)	50(3.95%)	**I,266**
PROFESSION											
DOCTORS	740(70.88%)	269(25.77%)	3(0.29%)	4(0.38%)	5(0.48%)	5(0.48%)	4(0.385)	7(0.67%)	2(0.19%)	5(0.48%)	**1,044(**
NURSES	880(63.08%)	369(26.45%)	30(2.15%)	30(2.15%)	20(1.43%)	25(1.79%)	13(0.93%)	12(0.86%)	3(0.22%)	13(0.93%)	**1,395**
PHARMACISTS	54(67.5%)	15(18.75%)	2(2.5%)	2(2.5%)	1(1.25%)	1(1.25%)	1(1.25%)	1(1.25%)	1(1.25%)	2(2.5%)	**80**
TOTAL OF HW POST REG	1674(66.46%)	653(25.92%)	35(1.39%)	36(1.43%)	26(1.03%)	31(1.23%)	18(0.71%)	20(0.79%)	6(0.24%)	20(0.79%)	**2,519**
OUT-PATIENT	186770(62.07%)	39825(13.24%)	8300(2.76%)	11000(3.66%)	10400(3.46%)	22717(7.55%)	5200(1.73%)	4903(1.63%)	5000(1.66%)	6800(2.26%)	**300,915**
IN-PATIENT	10974 (77.29%)	1979(13.94%)	410(2.89%)	60(0.42%)	68(0.48%)	513(3.61%)	48(0.34%)	76(0.54%)	10(0.07%)	61(0.43%)	**14,199**

OAUTHC: Obafemi Awolowo University Teaching Hospital Complex, LAUTECH: Ladoke Akintola University of Technology Teaching Hospital, SH-1: State Specialist Hospital Ede, SH-2: State Specialist Hospital, Ikire, SH-3: Specialist Hospital, Ikirun, SH-4: Specialist Hospital, Iwo, SH-5 Specialist Hospital Ila–Orangun, SH-6: Specialist Hospital Ile–Ife, SH-7: Specialist Hospital, Ipetu, SH-8: Specialist Hospital, Ilesa

Table 3: Analysis of WHO core Pharmacovigilance Process Indicators

Indicator item	Assessment questions	OAUT	LAUTE	SH-1	SH-2	SH-3	SH-4	SH-5	SH-6	SH-7	SH-8
CP1	ADR reports in (2018)	17	9	12	0	4	3	7	0	0	8
CP2	Reports (current total number) in the local database	76	49	23	2	11	15	13	4	nad	16
CP3	Percentage of total annual reports	0	0	0	0	0	0	0	0	0	0
CP4	Percentage reports subjected to casualty	0	0	0	0	0	0	0	0	0	0
CP5	Percentage completed and submitted to local PV centre	85.7	77.7	100	nad	nad	nad	nad	nad	nad	nad
CP5a	Percentage of reports committed to National PV centre database from the local PV centre	85.7	77.7	100	nad	nad	nad	nad	nad	nad	nad
CP6	Percentage reports of therapeutic failure	0	0	0	0	0	0	0	0	0	0
CP7	Percentage medication errors reported	0	0	0	0	0	0	0	0	0	0
CP8	Percentage of registered pharmaceutical industries with PV pharmacovigilance system.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CP9	Number of active surveillance activities initiated, ongoing or completed in the last five years	0	0	0	0	0	0	0	0	0	0

Key for Table 3: OAUTHC: Obafemi Awolowo University Teaching Hospital Complex, LAUTECH: Ladoke Akintola University of Technology Teaching Hospital, SH-1: State Specialist Hospital Ede, SH-2: State Specialist Hospital, Ikire, SH-3: Specialist Hospital, Ikirun, SH-4: Specialist Hospital, Iwo, SH-5 Specialist Hospital Ila–Orangun, SH-6: Specialist Hospital Ile–Ife, SH-7: Specialist Hospital, Ipetu, SH-8: Specialist Hospital, Ilesa, Nad: No available data, NA: Not available

Table 4: Analysis of WHO Core Outcome Pharmacovigilance Indicators

Indicator item	Assessment questions	OAUT	LAUTE	SH-1	SH-2	SH-3	SH-4	SH-5	SH-6	SH-7	SH-8
CO1	Number of signals generated in the last 5 years	0	0	0	0	0	0	0	0	0	0
CO2	Number of regulatory notifications issued in the last year	-0	0	0	0	0	0	0	0	0	0
CO3	Number of medicine -related hospital admissions per 1000 admissions	0.45	2.02	0	0	0	0	0	0	0	0
CO4	Number of medicine -related deaths per 1000 persons served the hospital per year	Inadq data	Inadq data	no data	no data	no data	no data	no data	no data	no data	no data
CO5	Number of medicine -related death per 1000 persons in the population	Inadq data	Inadq data	no data	no data	no data	no data	no data	no data	no data	no data
CO6	Average cost of treatment of medicine-related illnesses	Inadq data	Inadq data	no data	no data	no data	no data	no data	no data	no data	no data
CO7	Average duration (Days) of medicine-related illness	Inadq data	Inadq data	no data	no data	no data	no data	no data	no data	no data	no data
CO8	Average cost of medicine - related hospitalization.	Inadq data	Inadq data	no data	no data	no data	no data	no data	no data	no data	no data

Key for Table 4: OAUTHC: Obafemi Awolowo University Teaching Hospital Complex, LAUTECH: Ladoke Akintola University of Technology Teaching Hospital, SH-1: State Specialist Hospital Ede, SH-2: State Specialist Hospital, Ikire, SH-3: Specialist Hospital, Ikirun, SH-4: Specialist Hospital, Iwo, SH-5 Specialist Hospital Ila–Orangun, SH-6: Specialist Hospital Ile–Ife, SH-7: Specialist Hospital, Ipetu, SH-8: Specialist Hospital, Ilesa,
Inadq data: Inadequate data.

4. Discussion

The study of assessment of pharmacovigilance activities at secondary and tertiary health facilities in Osun state using WHO core pharmacovigilance indicators has revealed the area of weaknesses and strengths of pharmacovigilance in the assessed health facilities in the state as shown in Tables 1 and 2. Pharmacovigilance structures were not adequate especially in all the states' secondary health facilities. Therefore the existing facilities need to be upgraded to satisfy the healthcare need of the populace. Most importantly, efficient and functioning/functional Pharmacovigilance system having the WHO prescribed minimum requirements should be adopted[7]. This weakness is hampering Pharmacovigilance performance in the state. OAUTHC, Ile-Ife however, could boast of a pharmacovigilance structure, this may be due to it being a training facility center. Although, the same was not seen in LAUTECH Teaching Hospital, Osogbo. Also, it was observed that OAUTHC, Ile-Ife with highest number of patients turn out as in the Tables 1 and 2. It performed better in the state due to the general acceptance of the need for Pharmacovigilance in the facility and probably due to adequate number of staff available Tables 1 and 2. or willingness of the center to improve patient safety. The study revealed poor budgeting for pharmacovigilance in most of the centers. None of the centers had financial provision for pharmacovigilance. This was distinct from the findings in the University of Benin Teaching Hospital, Nigeria in which there was financial provision for the pharmacovigilance in the center[10]. It is important to fund pharmacovigilance as development of active pharmacovigilance program, provision of training; feedback information dissemination and maintenance of the centers are useful tools in pharmacovigilance that require adequate finances[10]. Although, facilities may have provision to set up pharmacovigilance systems it is only when those provisions are matched with a regular and sustainable budget that real action and long term planning can be achieved[11]. The entire state health facility studied attested to the fact that there is availability of standard reporting form. This is a pointer to the availability of one of pharmacovigilance most important tool necessary for spontaneous ADR reporting[12]. The processes and outcomes/impacts were however seen to be poor in all the state health facilities studied, perhaps due to lack of awareness of measuring indices for pharmacovigilance evaluation and monitoring. Pharmacovigilance centers should send their report to local data base for onward transmission to Uppsala Monitoring Centre (UMC) via National Pharmacovigilance Center. The above submission is being hindered by poor records keeping in all the facilities. This is not different from what others[13] found out as reasons for ADR under reporting in their studies. Therefore, it is imperative to take the pharmacovigilance system in the state out of their infancy and begin to do the needful for drug safety reasons. In the utilization of the WHO pharmacovigilance indicators, it is evident that the state health facilities have a long way to go to broaden the scope of reportable incidents. It is hoped that with proper implementation of Nigerian National Pharmacovigilance Policy, there would be a wider acceptance and dissemination of roles the hospitals are to play in the promotion of pharmacovigilance system. The indicators had exposed areas that need urgent intervention and modification in the health information system management in the state health facilities. The WHO indicators have proven to be quite useful in this assessment. However, just like submission[10], absence of trained pharmacovigilance personnel hindered the provision of results for the pharmacovigilance process indicators in all the centers. Accordingly, structural pharmacovigilance indicators failed to fully capture the functionality of pharmacovigilance system. There is also need for in-depth survey for derivation of outcome/impacts indicator, which young pharmacovigilance system is unable to execute. The need to develop a scoring system to quantify the indices in numerical terms to expose the deficiencies quantitatively is important for the operation of the indicators. Pharmacovigilance activities generally are related to every sector of pharmaceutical management framework such as: selection, procurement, distribution, use, management support and policy and for legal framework. Pharmacovigilance is also important because of limited safety experience prior to marketing authorization -animal testing, clinical trials. Therefore, there is a need for post marketing surveillance to establish the total risk due to all adverse drug reactions[14]. Nigeria being the most populous black nation with several genetic and racial differences therefore; adverse Reactions to Drugs in other countries may not be applicable to Nigeria. Furthermore, there is limited information available on Adverse Drugs Reactions (ADRs) in Nigeria[15] hence there is need to generate her own report[16].The need to build a useful safety information and database and improve quality of healthcare offered to the patient is essential in all strata of healthcare system as emphasized[15]. It is interesting to note that Osun state, like others 36 states in Nigeria, reports its ADRs using ADR forms. Lagos University Teaching Hospital (LUTH)

coordinates the pharmacovigilance activities of the south west states including Osun state. The state benefits regularly from the quarterly newsletter from the NPC, Abuja while the signals generated from the state are collated at the state NAFDAC office, Osogbo before same is forwarded to the Zonal centers, LUTH for onward transmission to National headquarter,Abuja[15]. The pharmacovigilance growth in Nigeria can be traced to the role of NAFDAC, the formulation of Nigeria National Drug Policy in 2005 and the drug safety Pharmacovigilance Policy Document of 2012. Evaluation of pharmacovigilance awareness and practices especially among health workers have been carried out across the nation in the South-East, South-West and in the North-West by notable scholars. Pharmacovigilance activities in these zones were found to be at infancy state[16,17]despite that, there was revealed high level of awareness of pharmacovigilance by all the health care providers in Nigeria[18,19]. At the 5th Pharmacovigilance summit, 8-29 April 2016 Dubai UAE, Samirah, Saleh in reviewing the importance of ADRs, reported that 337 pharmaceutical products recalls in 2014, a 7% increase over 2013 (315 recalls), and up to 16% from 2012 (291recalls). According to him examples of licensed drugs withdrawn after marketing for safety reasons: Thalidomide (1965)-phocomelia; practolol(1975)-sclerosing; Phenformin(1982)-lacticacidosis;Veralipride(2007)-depression; Troglitazone (2000)-hepatitis and rosiglitazone (2010)-risk of myocardial infarction and death. It was further showed that early detection and reporting of ADRs can minimize and promote medicinal safety. The report[20] titled: "Pharmacovigilance: Process of detection assessment understanding and prevention of ADR" pinned its (ADR) importance by quoting the submission of a legend Mathew Prior (1664-1721) "I was cured yesterday of my disease, I died last night of my physician". Spontaneous and voluntary reporting of ADRs remain the most important pharmacovigilance strategies to prevent and control it (ADRs) within the health care system[21]. In principle and practice, passive surveillance involves spontaneous reports i.e. an unsolicited communication by healthcare professionals or consumers to a Pharmacovigilance center (National, regulatory authority) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and is not from a study or any organized data collection scheme. Active Surveillance seeks to ascertain completely the number of adverse events via a continuous pre-organized process. An example is the follow-up of patients treated by a particular drug as in cohort event monitoring and drug event monitoring while Stimulated Reporting include several methods used such as one-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a predesigned case function. ADR can also be reported electronically through PRASCOR (Pharmacovigilance Rapid Alert System for Consumer Reporting). This short code service introduced for consumers to alert NAFDAC on safety and quality issue via SMS to 20543 for free on MTN, Etisalat and GLO. This electronic tool reduces substandard and falsified medical products which are major contributor to ADR in our setting[15]. Under Reporting: While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment and is indispensable for signal detection. The need for more active surveillance has also become increasingly clear. Without information on utilization and extent of consumption, spontaneous reports are unable to determine the frequency of an ADR attribution to a product or its safety in relation to a compatriot. Other scholars like Ogundele *et al.,* (2012) also noted inappropriate structures; deficient processes especially at the facility level may also contribute to the poor reporting rate. Leakages, contradictory information and insufficient laboratory findings are among identified obstacles to efficient reporting[13].

5. Conclusion

The structure and process of pharmacovigilance in both the tertiary and secondary health facilities in the state is at low level resulting in poor outcome which is not in line with recommendation by the regulatory bodies. Proactive surveillance program is therefore suggested to be the focus and interest of all stakeholders in health delivery in Osun state for drug safety. The itemized indicators in the study have given the centers/facilities studied poor scores. There is need to do further self-appraisal that will further facilitate their involvement in other measure to rescue or control lapses or deficiencies towards improving the quality and quantity of ADR reports. It is imperative to inculcate a more articulate approach to routine approach for data gathering and documentation into the health care system in the state. The Hospitals in Osun State have inadequate Pharmacovigilance structures with poor financial sustenance. The processes and outcome impact in these hospitals are poor due to their poor documentation of pharmacovigilance activities. Suggestions such as incorporation of pharmacovigilance into curriculum, budgetary allocation, training and retraining in orientation programme and development of an organogram that

incorporate the Therapeutic Drug Committee should be adopted.

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