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Adverse Drug Reactions Monitoring in the Northern Region of Zambia

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***Abstract*—**The Copperbelt University Health Services (CBUHS) was designated by the Zambia Medicines Regulatory Authority (ZAMRA), formally the Pharmaceutical Regulatory Authority (PRA) as a regional pharmacovigilance centre to carryout activities of drug safety monitoring in four provinces in Zambia. CBUHS's mandate included stimulating the reporting of adverse drug reactions (ADRs), as well as collecting and collating ADR reports from health institutions in the four provinces. This report covers the researchers' experiences from May 2008 to September, 2016. The main objectives are 1) to monitor ADRs in the Zambian population, 2) to disseminate information to all health professionals in the region advising that the CBU health was a centre for reporting ADRs in the region, 3) to monitor polypharmacy as well as the benefit-risk profile of medicines, 4) to generate independent, evidence based recommendations on the safety of medicines, 5) to support ZAMRA in formulating safety related regulatory decisions for medicines, and 6) to communicate findings with all key stakeholders. The methodology involved monthly visits, beginning in early May 2008 to September, 2016, by the CBUHS to health institutions in the programme areas. Activities included holding discussions with health workers, distribution of ADR forms and collection of ADRs reports. These reports, once collected, were documented and assessed at the CBUHS. A report was then prepared for ZAMRA on quarterly basis. At ZAMRA, serious ADRs were noted and recommendations made to the Ministry of Health of the Republic of Zambia. The results show that 2,600 ADRs reports were received at the pharmacovigilance regional centre. Most of the ADRs reports that received were due to antiretroviral drugs, as well as a few from anti-malarial drugs like Artemether/Lumefantrine – Coartem®. Three hundred and twelve ADRs were entered in the Uppsala Monitoring Centre WHO Vigiflow for further analysis. It was concluded that in general, 2008-16 were exciting years for the pharmacovigilance group at CBUHS. From a very tentative beginning, a lot of strides were made and contacts established with healthcare facilities in the region. The researchers were encouraged by the support received from the Copperbelt University management, the motivation provided by ZAMRA and most importantly the enthusiasm of health workers in all the health care facilities visited. As a centre for drug safety in Zambia, the results show it achieves its objectives for monitoring ADRs, Pharmacovigilance (drug safety monitoring), and activities of monitoring ADRs as well as preventing them. However, the centre faces critical challenges caused by erratic funding that prevents the smooth running of the programme.

***Keywords*—**Assessments, evaluation, monitoring, pharmacovigilance.

I. Introduction

AN ADR is a response to a medicine which is noxious and unintended, which occurs at doses normally used in the treatment of humans. It may occur following a single dose or prolonged administration of a drug, or result from the combination of two or more drugs. It is a special type in which a causative relationship can be shown [1]. The therapeutic ineffectiveness is a frequent drug-related problem that occurs in a variety of different situations and different mechanisms can cause it.

In 2008, the ZAMRA, formally PRA of the Ministry of Health of Zambia, appointed the CBUHS to take up the role of co-coordinating ADR activities on their behalf in provinces consisting of the northern region of the country (Copperbelt, Luapula, Northern, North Western and Western Provinces) [7]. ZAMRA is the statutory national medicines regulatory body for Zambia established under the Medicines and Allied Substances Act of 2013. The authority regulates all the medicines and allied substances that enter the country. ZAMRA, therefore, has the responsibility of, among other things, regulating medicines for public health protection as well as monitoring drug safety [5]. CBUHS was chosen to carry out the programme because of its central location and its active involvement in ADR monitoring (pharmacovigilance) activities. The main function of the CBUHS in the national pharmacovigilance programme had been to collect and collate all ADRs reports from health institutions based in the four provinces of Zambia. These provinces included Copperbelt, North-western, Luapula and Western. However, the focus of this study was the Copperbelt and North Western provinces. Reports of the researchers' activities and findings were prepared and presented on quarterly basis to ZAMRA in Lusaka, Zambia [7].

II. Objectives

The objectives of the CBUHS include:

- To coordinate ADRs activities in northern region of Zambia.
- To conduct in-service trainings for healthcare workers on the significance of reporting ADRs.
- To promote rational drug use and avoid Polypharmacy.
- To advise ZAMRA on our findings, and make recommendations on the safety of medicines.
- To make linkages with other partners working on drug safety monitoring.
- To draft the ZAMRA medicine monitoring magazines for information dissemination to all healthcare workers
- To have a pharmacovigilance regional centre that will be recognized by the Uppsala Monitoring Centre.
- To acknowledge and give feedback to the reporters on the ADR reports received.

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III. Methodology

After receiving authorization from ZAMRA for the CBUHS to co-ordinate ADRs activities on its behalf, the prospective approach was adopted to collect ADR reports from all health institutions, initially in the Copperbelt [7].

The main approach adopted by the CBUHS Drug Safety Monitoring team was to conduct visitations to all health institutions in the province by once every three months to collect the ADR reports, and also to identify those key health professionals for the programme to run successfully [8]. In addition to visiting the various institutions, CBUHS also provided linkages with international drug monitoring agencies such as the World Health Organization (WHO) collaborating centre on international drug monitoring based in Uppsala, Sweden [7].

The major stakeholders were pharmacist's in-charge, medical doctors, pharmacy technologists and nurse's in–charge. Hospital pharmacy departments were the sections targeted as being the logical central point in the facility for health professionals to report an ADR [8]. Arrangements were made in each hospital for all ADR filled reports from wards and clinics to be collected at the pharmacy department [2].

Over two thousand six hundred (2600) ADR reports were collected up to September 2016. Upon collection of the ADR reports, the CBUHS Drug Safety Monitoring Team performed the following tasks:

1. Record the data from the ADR's reports collected in the ADVERSE DRUG REACTIONS REGISTER (ADRR), which is maintained at our facility. The data entered in the ADRR include:

a. Date of the report;
b. Name of the institution where the ADR report originated;
c. Name of the medical professional making the report;
d. Date of birth, age of the patient;
e. Adverse reactions recorded;
f. Details of the onset of the reaction;
g. Details of the suspected drugs;
h. Details of the outcome of the reaction; and
i. Assessment and feedback.

2. Assess the quality of the ADR reports received for completeness and accuracy to ensure that the minimum information criteria required for reporting were met. The team then prepared a summary of the quality of ADR reporting quarterly to ZAMRA [1]. If an ADR report met the required minimum information criteria, it was entered in the WHO Uppsala Monitoring Centre online Vigiflow system by the CBUHS pharmacovigilance team and validated.
3. Evaluation of the expectedness of ADRs was done (e.g., whether the nature, severity and specificity of the reported adverse reaction were consistent with the adverse reaction terms mentioned in the standard text of Martindale: The Complete Drug Reference & Physician's Desk Reference [3].
4. A causality assessment report based on the WHO causality assessment grading was prepared.
5. All the reports including the causality assessment reports were further reviewed and analyzed.
6. A number of each ADR report were assigned i.e. 0001/2008, 0002/2008, and so on [8].
7. A report is then compiled to ZAMRA based on the ADR reports received.

IV. Findings

A total of 21 health facilities were visited during the period. The facilities visited included government hospitals, those owned by the mines and district health services in the Copperbelt and North Western Province. All the ADR reports that were collected and received at the centre were documented and kept at CBUHS.

A. Quality of ADR Reporting

The overall assessment of ADR reports revealed that the quality of data was satisfactory. However, some gaps existed and attempts were made to resolve those. Of the 2600 ADR reports received from health institutions, only 312 (12%) reports were complete enough for entry in Vigiflow [4], i.e., having minimum information for reporting including patient details, ADR details, drug details and reporter details.

The quality of ADR reporting was partly affected due to gaps in the ADR reporting form itself, i.e., critical data fields regarding start and/or stop dates of adverse reaction, relevant medical history, past drug history, and re-challenge/de-challenge information were missing. Without the start & stop dates of adverse events, it was not possible to discern the status of temporal relationship and de-challenge test. Hence, it was presumed that the adverse event(s) occurred when a patient was on suspect drug(s) while attempting the analyses of ADR reports [3]. However, *some of these gaps hindered from committing of reports into the Vigiflow*. In addition, the quality of ADR reporting was affected by deficient reporting by the medical professionals, even when the ADR form had data field(s) to fill in the required information. Details of missing information included start and/or stop dates of suspect drug(s) intake, dose of suspect drug(s), weight of patient, treatment of ADR(s), year of birth, etc. This is not surprising as in most of the African countries, ADR reporting is allowed through various levels of healthcare professionals a situation which may affect the quality of reporting in the absence of proper training, especially regarding mandatory fields. Besides, patients too in some instances may not remember specific start/stop dates of drug intake and adverse events, treatment taken, or other relevant details, etc., which affect the reporting quality. It was also not uncommon to miss out specific birth years, since the proportion of women delivering at health institutions can be quite low in our country, and in this culture birth certificates are often uncommon [3].

B. Evaluation and Analysis of ADRs

An evaluation and analysis of the adverse events in 2,600 ADR reports related to use of anti-retroviral and miscellaneous drug(s) or drug combination(s) were carried out. Most of the adverse reactions reports collected at CBUHS

pharmacovigilance centre were due to anti-retroviral drugs, while others were due to anti-tuberculosis drugs as well as on product quality problem. Table I shows the adverse reaction and their causative agents [3].

TABLE I
ADRS VS. CAUSATIVE AGENTS

Adverse Events	Causative Agent(s)	No. of Cases
1. Peripheral neuropathy	Stavudine/Lamivudine	724(27.8%)
2. Anaemia	Zidovudine	120 (4.6%)
3. Skin rash	Nevirapine	422(16.2%)
4. Treatment failure	Triomune-40	176(6.8%)
5. Dizziness/headache/psychosis	Stavudine/Lamivudine	217(8.3%)
6. Heart Palpitations	Emtricitabine/Tenofovir	119(4.6%)
7. Diarrhoea	Emtricitabine/Tenofovir	208(8.0%)
8. Itching rash	Nevirapine	220(8.5%)
9. Renal stone formation	Indinavir	18(0.7%)
10.Allergic reactions	Nevirapine/cotrimoxazole	219(8.4%)
11.Lipodystrophy	Stavudine	116(4.5%)
12.Teratogenic in pregnancy	Efavirenz	41(1.6%)

The ADR reports were entered onto the Vigiflow database, followed by generation of output reports and causality assessments for individual cases. Each ADR report, the corresponding Vigiflow output report and the summary of causality assessment are presented respectively.

Almost all adverse events were as expected. The unexpected events noted were: a) development of breast enlargement and swelling of face related to use of stavudine+lamivudine and nevirapine, b) development of sores on limbs and mouth, and swelling of hands and legs related to use of nevirapine and lamivudine, and c) development of bone marrow depression related to the use of efavirenz. These results required further evaluation [3]. Overall, it must be emphasized that the number of ADR reports analyzed were not enough to make definite conclusions regarding the relationship between the drug(s) and adverse event(s). Similarly, no conclusion was drawn regarding the nature, incidence and severity of these adverse events. However, despite the small numbers, there is valuable information determined which drug(s) and associated adverse event(s) require further assessment [3].

C. Assessment of ADR Reporting Capacity

Zambia has a dedicated Pharmacovigilance department for managing and coordinating drug safety monitoring since June 2006, when it was officially launched. It became an associate member in 2004 and finally in March 2010 became a full member (97th full member) of the WHO Programme for International Drug Monitoring due to the efforts made by the regional centre to drive the activity since 2008. However, in addition to the sub-optimal performance concerning ADR data collection, processing and analysis of the few existing reports in Vigiflow started in late 2009 [3].

D. Current and Future Challenges

The main challenges for the pharmacovigilance programme were:

i) Generation of a sufficient number of ADR reports relative to the population due to the low reporting level.

Within the WHO Programme, the optimal National Pharmacovigilance Centre is expected to ideally send over 200 reports per million inhabitants per year in addition to adherence to other standards. This project clearly demonstrated that in the years 2008-16, the ADR report collection in Zambia was as low as 2,600—thereby, achieving only less than 2% of the desired target, as illustrated in the Table II [3].

TABLE II
ZAMBIA'S POPULATION AND EXPECTED % OF ADRS

Country	Population (Million)	Target ADRs (at 200 per million per year)	Actual reports collected in 2008-16 (or in most recent year, or since inception of pharmacovigilance program)	% of target achieved
Zambia	14.54	2,384	2,600	Less than 2%

ii) Entering and analyzing ADR data regularly and to avoid potential backlog of ADRs as well as financial resources to run the programme.
iii) Lack of country database to manage the ADRs reports collected and received [3].
iv) To train and maintain a pharmacovigilance team that can implement and manage a pharmacovigilance program over several years, including timely ADR data entry/analysis and sharing of information with appropriate authorities.
v) Lack of interest to report ADRs from health professionals [3].

V. CONCLUSION

ADR monitoring in Zambia has come to stay with the help of government support and other cooperating partners in the pharmacovigilance programme. As a centre for drug safety, we ensured that we achieve our objectives to monitor ADRs in Zambia.

There had been some level of drug safety monitoring activity in Zambia; however, this activity had not been consistent due to lack of financial resources to support the pilot project. Whilst data collection appeared to be ongoing, data processing and analysis were yet to be explored. There was also very little data dissemination back to the health professionals making them to lose interest in reporting ADRs.

Pharmacovigilance is a global science which requires collaboration between countries and various technical international organizations. These organization include WHO, Uppsala Monitoring Centre (UMC), Uppsala Monitoring Centre - Africa (UMC-A) and other cooperating partners [6]. Sharing of individual case safety reports at the global level leads to the generation of drug safety signals which may then be further analyzed and strengthened. Whilst we were keen to

develop pharmacovigilance systems in Zambia, it was obvious that our capacity was still weak and required strengthening. Building capacity in all areas of pharmacovigilance - data collection, management, analysis and dissemination - usually takes time. However, it was possible to partner with and learn from established institutions or innovative initiatives like AMC-Africa to make full use of country data. Thereafter, the collaboration will naturally evolve and take on other forms including assistance with research in pharmacovigilance and pharmacoepidemiological methods. Signal generation from spontaneous reporting was just one part of the system that ensured patient safety. Signal strengthening, identification of system and risk factors and appropriate communications were all the factors that the ZAMRA was trying to address. While ZAMRA had documented the reporting of ADRs system online on its website, the main challenge was still the under reporting of ADRs from health professionals countrywide.

Pharmacovigilance (drug safety monitoring) have come to stay in Zambia thanks to government support, strong public health programmes "the big three (HIV/AIDS, malaria and Tuberculosis)", good local and international linkages such as the Ministry of health (MoH), WHO, UMC, UMC-Africa, health professionals from provinces and districts, the stable political situation of our country as well as availability of some resources from the global fund to support drug safety.

VI. Recommendations

In order to improve the pharmacovigilance programme in the region as well as for the country, the following measures should be adopted in future:

i) Continued sensitization workshops for healthcare workers for pharmacovigilance.
ii) Source for reliable funding for pharmacovigilance programme from global funds and other partners.
iii) Promote public awareness of drug safety issues.
iv) ADR report forms should be made readily available in all health institutions.
v) Provide feedback to healthcare professionals for all ADRs reported to the national pharmacovigilance unit.

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