MEDICINES BULLETIN

Medicines Control Authority of Zimbabwe: Vol 1, January 2018

1. VACCINE PHARMACOVIGILANCE

R. Ndemera

Vaccine pharmacovigillence is a critical aspect in public health and a key indicator for pharmacovigilance systems. The MCAZ in collaboration with the Expanded Programme on Immunisation- Ministry of Health and Child Care (EPI-MoHCC), have continuously worked to develop vaccine pharmacovigilance in Zimbabwe through participation in World Health Organisation (WHO) projects, development and implementation of the Adverse Events Following Immunisation (AEFI) surveillance guidelines and conducting trainings for health care professionals on AEFI reporting and case investigations.

In 2017, Zimbabwe participated in a study titled '**Inter-country study to assess the inter-rater reliability of the WHO AEFI causality assessment methodology and the utility of the new WHO AEFI causality assessment software.'** Zimbabwe and India were the two participating countries in the study, and was conducted under the oversight of the World Health Organization (WHO), Global Advisory Committee on Vaccine Safety (GACVS).

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1. VACCINE PHARMACOVIGILANCE

R. Ndemera

Fig 1: Zimbabwe Project Team (AEFI National Committee members & experts, WHO, EPI-MoHCC, & MCAZ)

Summary of Study protocol Background:

Causality assessment is a method used to determine the relationship, and the degree of the relationship, between a medicine or vaccine and an adverse event or reaction that would have precipitated following administration of the medicine or vaccine.

Problem statement: Feedback from end users and critics of the AEFI causality assessment methodology indicated that the methodology by itself has unanswered questions regarding its rationality in the present rapidly changing global scenario and that there is lack of validation regarding the inter-raters agreement in final classification in the methodology. An editorial in "Expert Review of Vaccines" indicated that there was no evidence in literature about the analysis and the use of AEFI assessment procedures.

There is no information or reports on AEFI surveillance that uses the WHO AEFI causality assessment method. This adds to the doubts about vaccine safety and lack of surveillance of AEFI which are the most frequent themes proposed by anti-vaccination movements.

Justification of study: To address the above aspects, the study evaluates two features:

The methodology developed by WHO will be evaluated for reliability (the degree to which an assessment tool produces consistent results between country evaluators (Consistent = high kappa > 0.6 score INTRA and INTER rater agreement)

As a part of the assessment, the manual AEFI causality assessment methodology will be compared to the electronic methodology and evaluated for usability (considered as good agreement if kappa > 0.6 score between the manual and electronic approaches)

Research question: Is the revised methodology for causality assessment of AEFI developed by WHO reliable?

Study Objectives

To determine the reliability and level of agreement in final classification of the revised WHO methodology for causality assessment of Adverse Events Following Immunization (AEFI).

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Fig 2: India-Zimbabwe inter –country assessment of the WHO AEFI causality electronic tool held on 24th to 30th April 2017 in Delhi India.

Qualitative assessment of usability between manual and electronic system among teams from the two countries.

Two workshops were conducted; **Zimbabwe Intra Country assessment of the WHO AEFI causality manual tool workshop** held on 6th to 10th March 2017 at WHO Country Office, and the **India-Zimbabwe inter –country assessment of the WHO AEFI causality electronic tool** held on 24th to 30th of April 2017 in Delhi India. The objectives of the workshops were to determine the reliability and level of agreement in final classification of the revised WHO manual and electronic methodology for causality assessment of AEFI. This included independent assessment of a total of 250 anonymised cases of serious AEFI that have been reported in Zimbabwe (75 cases) and India (175 cases).

The assessment results for the 250 cases were collected by the WHO/HQ Global Vaccine Safety Initiative (GSVI) for further in-depth statistical analysis using Kappa method, in accordance with the protocol. It was agreed that a joint manuscript on the study findings would be written, and a presentation on the quantitative and qualitative findings was done at the GAVCS meeting held on the 6th of December 2017.

It was also agreed at the Zimbabwe Intra Country assessment workshop, that a descriptive case study manuscript would be written, so as to publish the quality AEFI cases data as it was considered very important vaccine safety information to disseminate.

Acknowledgement with thanks is given to all the MoHCC, WHO Country Office Zimbabwe, WHO Afro Region, WHO HQ, GACVS, India INCLEN, India Ministry of Health, India WHO Country Office, EPI- MoHCC, and all study protocol team.

2. HIGHLIGHTS FROM TARGETED SPONTANEOUS REPORTING PROGRAMME 2017 TRAININGS

Y.T Mvududu

The Targeted Spontaneous Reporting (TSR) of essential medicines has been implemented in Zimbabwe in most public and some private health care institutions. The success of the pilot phase from October 2012 to September 2013 resulted in the need to expand the programme beyond ARVs and anti-TB medications. The program now enables reporting of adverse drug reactions of essential medicines in the Essential Drugs List in Zimbabwe (EDLIZ).

The Pharmacovigilance and Clinical Trials Division conducted 8 TSR trainings of health care professionals in 2017. The aim of the trainings was to educate, encourage and remind all health care professionals to continuously participate effectively in the reporting of Adverse Drug Reactions (ADRs), and preparation of setting up regional sentinel sites. Amongst the health care professionals trained were District Medical Officers (DMO), District Health Information Officers (DHIO), nurses, doctors and pharmacy personnel.

The figure below indicates the total number of TSR reports received by the MCAZ and the reporting professionals.

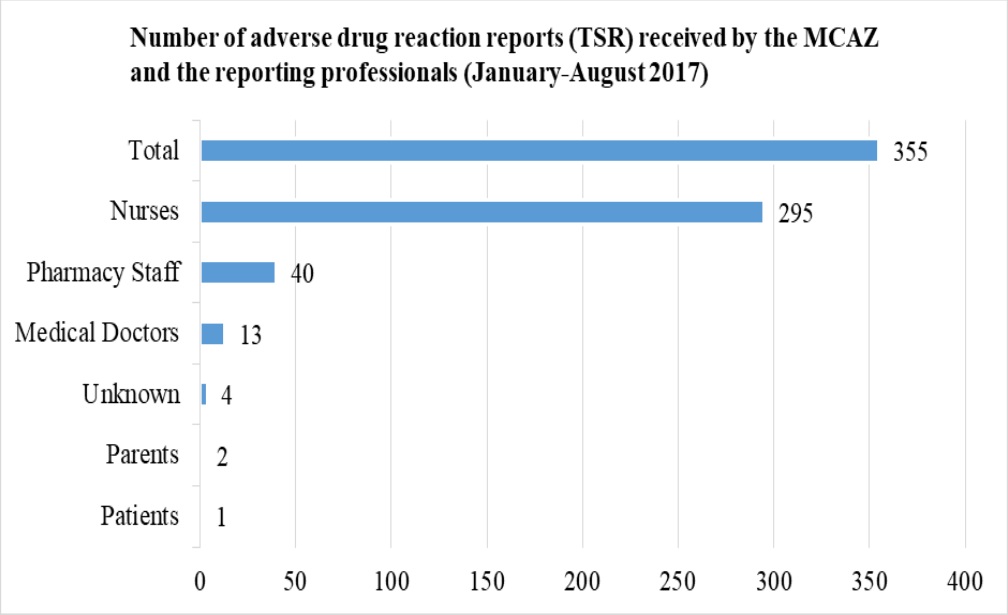

Fig 1:Number of ADR reports received from the TSR programme by the MCAZ (January-August 2017)

Of the 355 reports received during the period January-August 2017, 83% were reported by nurses.

The graph below shows 15 of the most frequently reported of adverse drug reactions that were received by the MCAZ from January to September 2017. A total of 466 adverse drug reaction cases were received and of these, 26% were gynaecomastia cases associated with efavirenz .

2. HIGHLIGHTS FROM TARGETED SPONTANEOUS REPORTING PROGRAMME 2017 TRAININGS

Y.T Mvududu

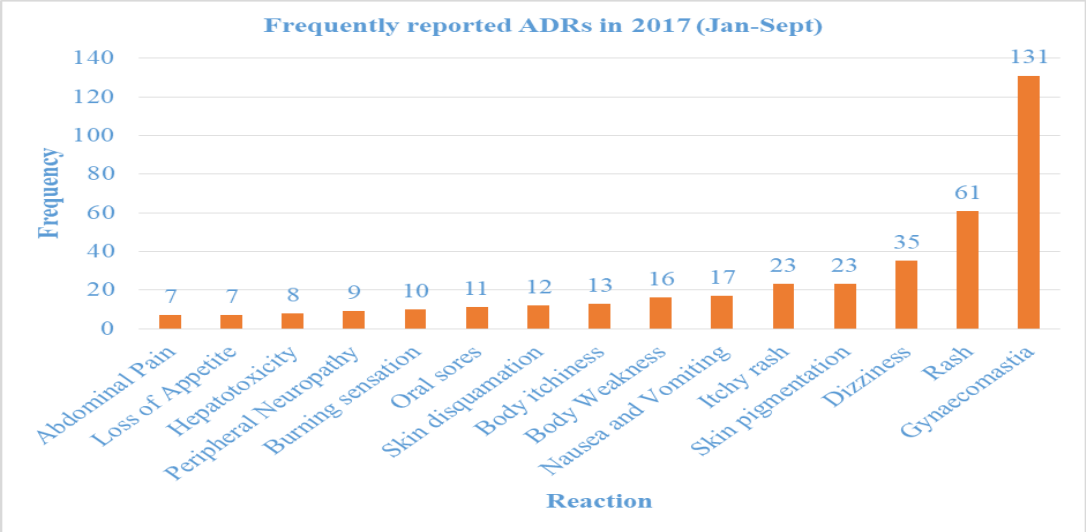

Fig 2: The graph shows 15 of the most frequently reported Reactions that were received during the January to September 2017. Gynaecomastia continues to be the most frequently reported ADR.

All reports are evaluated for causality assessment by the Medicines Control Authority of Zimbabwe (MCAZ). Reporters were sent feedback on the assessments. In the previous edition of the bulletin, Volume 1, May 2017, three articles were included on the information gathered from these reports. These were of reports for gynaecomastia from patients on Efavirenz, renal impairment from patients on Tenofovir and unintended pregnancies in women on Efavirenz based regimens with Levornogestrel implants.

Part of the curriculum for the trainings was educating participants on the new electronic reporting system. The participants welcomed this as a positive development. However, the participants highlighted some areas for improvement that included a function to add supporting documents if any and to include a section were the batch numbers of the suspected medicines can be recorded.

Participants asked about the position of MCAZ on regulation of complementary medicines. The MCAZ staff advised participants that the regulations for complementary were now in place and MCAZ has started to regulate complementary medicines. The regulations can be found on the MCAZ website. Participants were also encouraged to report adverse events due to these complementary medicines.

Participants also communicated their concerns over the widespread selling of medicines on the streets and also suggested that in addition to the work the MCAZ is currently doing, they should invest in educating the public on the dangers of buying medicines from unapproved sources. Participants were informed that the MCAZ had established a public relations team which inclusive of other duties, were raising public awareness and educating the public on the importance of buying medicines from registered pharmacies. Participants also agreed that the onus is also on the health care professionals to advise patients to buy medicines from approved pharmacies. It was concluded that to combat the matter of patients buying medicines from the unapproved sources, collaborative efforts of the MCAZ and other stakeholders which include the health care professionals and the public is required. The participants indicated that the trainings were very informative and requested for future refresher trainings.

3. COMPARISON OF ADVERSE DRUG REACTION PROFILES IN PATIENTS ON ANTIRETROVIRAL AND ANTI-TUBERCULAR TREATMENT IN ZIMBABWE

Clinical Drug Investigation January 2018, Volume 38, Issue 1, pp 9–17

Josiah T. Masuka, Precious Chipangura, Priscilla P. Nyambayo, Andy Stergachis, Star Khoza

The Pharmacovigilance and Clinical Trial is proud to share with you an abstract from an article that was recently published from the TSR Programme. The Article was first published online on the 30th of September 2017 in the Clinical Drug Investigation Journal.

Abstract

Introduction

Few studies describe the adverse drug event profiles in patients simultaneously receiving antiretroviral and anti-tubercular medicines in resource-limited countries.

Objectives

To describe and compare the adverse drug reaction profiles in patients on highly active antiretroviral therapy only (HAART), HAART and isoniazid preventive therapy (HHART), and HAART and anti-tubercular treatment (ATTHAART).

Methods

We analysed individual case safety reports (ICSRs) for patients on antiretroviral therapy and anti-tubercular treatment submitted to the national pharmacovigillence centre during the targeted spontaneous reporting (TSR) programme from 1 September 2012 through 31 August 2016. All reports considered certain, probable or possible were included in the analysis.

Results

A total of 1076 ICSRs were included in the analysis. Most of the reports were from the HAART only group (n = 882; 82.0%), followed by patients on HHART (n = 132; 12.3%), and ATTHAART (n = 62; 5.7%). The ATTHAART (35.5%) and HHAART (34.1%) had a higher frequency of hepatic disorders than the HAART group (5.0%) (p\0.0001). A higher frequency of rash was reported in the HHAART (35.6%) and HAART groups (29.4%) than the ATTHAART group (14.5%) (p = 0.011).

Peripheral neuropathy occurred more frequently in the ATTHAART group (19.3%) than other groups (p = 0.001) while Stevens-Johnson syndrome (14.7%; p\0.001), gynaecomastia (18.2%; p\0.001), and lipodystrophy(4.5%; p = 0.012) occurred more frequently in the HAART group. The HHAART group was associated with a higher frequency of psychosis (4.5%; p = 0.002).

Conclusion

Antiretroviral therapy was associated with a higher frequency of Stevens-Johnson syndrome, gynaecomastia and lipodystrophy. Co-administration of antiretroviral and anti-tubercular medicines was associated with a higher frequency of drug-induced liver injury and peripheral neuropathy. Similarly, co-administration of isoniazid preventive therapy and antiretroviral drugs was associated with a higher risk for psychosis. There is a need to carefully manage TB/HIV co-infected patients, due to the higher risk of adverse drug reactions which may lead to poor treatment adherence and outcomes.

Copies of the publication have been circulated to PMDs, PNOs DMO, DNOs , PPs and all participants from the TSR programme.

READ THE FULL ARTICLE ONLINE in the:

Clinical Drug Investigation Journal on the following Link: https://link.springer.com/article/10.1007/s40261-017-0579-z

4. MCAZ GOOD CLINICAL PRACTICE (GCP) GUIDELINES CHANGES TO EXPECT

C. Mututa, N.K.A Muzangaza

The MCAZ published the first edition of the Good Clinical Practice (GCP) Guidelines to be used in clinical research in Zimbabwe in 2012. Since then the research area has rapidly evolved with a large number of clinical trial being conducted in Zimbabwe. The proposed amendments have resulted in the guidelines being separated into two parts : Part I *Guidelines for Good Clinical Practice in Zimbabwe* and Part II - *Guidelines for Application for Clinical Trials in Zimbabwe*.

The proposed guidelines start by describing the various phases of clinical trials in an effort to guide applicants on understanding what phase their trial falls under. The proposed changes include the replacement of the term **subjects with participants**, for individuals who are participating in the clinical trial to align with global terminology for clinical trials.

ICH E6 Good Clinical Practice is an international scientific and ethical quality standard for conducting, designing, recording and reporting trials involving human participation. It provides the public with assurance that all rights and safety of trial participants are protected and consistent with the principles that originate in the Declaration of Helsinki and clinical data. To address the concerns from GCP regulatory inspections in June 2015, the ICH released an amended version of the international guidelines for GCP: ICH GCP E6 (R2). The new GCP draft represents the biggest revision of the international ICH GCP guidelines for over 20 years, and has the potential to fundamentally alter the way in which clinical research is managed. The ICH E6 document is one of the main reference documents that was used to develop the Zimbabwean GCP Guidelines. The changes have been incorporated into the second edition of the guidelines. The major sections that have been updated include**: Investigator Responsibilities, Adequate Resources, Records and Reports, Sponsor, Quality Management, CRO, Trial Management, Data Handling and Record Keeping.**

A section on HIV/ AIDS Clinical and Epidemiological research, and HIV Preventive clinical trial has been added. The update comes as a result of the increase in HIV/AIDS related clinical and epidemiological, and preventive trials. These trials include advances in anti-retroviral therapy, which has influenced the clinical course of HIV infection, reduced mother to child HIV transmission and HIV transmission following occupational exposure to HIV. HIV related clinical research includes strategies to prevent HIV infection (i.e. vaginal microbicides) and to investigate medications that may increase the risk of HIV infection (i.e. long acting progestins). Guidance points have been added according to Ethical Considerations in Biomedical HIV prevention trials developed by the NAIDS and WHO.

Community Engagement and Communication has been added to include the establishment Community Advisory Groups (CAGs), a community representing body that may advocate for human rights and promote ethical conduct in clinical research; contribute to addressing and resolving grievances about the research process; give advice on accrual and retention of trial participants and voice concerns around the development, implementation and outcomes of specific clinical and related studies.

An **Online application platform and Clinical Trial Registry** has been developed and is expected to be piloted and introduced during the first quarter of 2018. MCAZ intends to host a familiarization workshop for researchers on the new system.

The draft guidelines will be circulated for comments by stakeholders involved in clinical research. We look forward to receiving your comments.

5. NEW MCAZ REPORTING TOOLS

T. Nyengerai

INTRODUCTION

The mandate of the Medicines Control Authority of Zimbabwe (MCAZ) is to protect public and animal health by ensuring that medicines and medical devices are safe, effective and of good quality. For the purpose of ensuring safety, the MCAZ is responsible for monitoring all adverse reactions or events related to medicines, vaccines and medical devices. The Pharmacovigilance and Clinical Trials Division (PVCT) of the MCAZ has established a reporting system for all adverse drug reactions or events. Information received from reporters is treated as confidential. In line with this objective, the MCAZ has been receiving an increasing number of reports and wishes to acknowledge with thanks the support for pharmacovigilance activities in Zimbabwe by the reporters including patients, nurses, medical doctors and pharmacists.

Individual Case Safety Reporting

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. Successful implementation or failure of pharmacovigilance activities depends on the reporting rate and quality of reports. These reports are submitted using individual case safety reporting (ICSR) forms. An ICSR is an adverse event report for an individual patient and is the source of data in pharmacovigilance.

MCAZ Reporting Tools

Pharmacovigilance reporting tools are the instruments employed by the MCAZ for collection of ICSR data. These tools are available in different formats and are effective in the implementation of pharmacovigilance activities. They are used for reporting of adverse drug reactions (ADRs), adverse events following immunisation (AEFI), serious adverse events / adverse events (SAEs/AEs) and medicinal product defects. These tools include the following:

e-ADR report from the MCAZ website hyperlink

- http://www.mcaz.co.zw/index.php/2016-01-08-06-40-00/e-reporting

Electronic copies available on the MCAZ website for download on the following hyperlinks:

Adverse Drug Reaction (ADR) Reporting form (PDF)

- http://www.mcaz.co.zw/index.php/downloads/file/151-adr-reporting-form

Medicinal Product defect form (PDF)

- http://www.mcaz.co.zw/index.php/downloads/file/107-product-defect-form

ADR and AEFI reports hard copies distributed to centres and also available for collection at MCAZ

MRCZ – MCAZ serious adverse events (SAE / AE) reporting form

- http://www.mcaz.co.zw/index.php/downloads/file/112-serious-adverse-events-report-form

The MCAZ encourages healthcare professionals and patients to make use of these forms for reporting adverse drug reactions / events. All reports received by the MCAZ are processed and uploaded on the World Health Organization (WHO) database (VigiBase) for further analysis. VigiBase enables comparison of pharmacovigilance data between national populations and is maintained and developed by the Uppsala Monitoring Centre (UMC) on behalf of the WHO.

5. NEW MCAZ REPORTING TOOLS

T. Nyengerai

Reporters are recommended to submit reports with complete information. The WHO - UMC measures the quality and amount of information from all national centers using the VigiGrade completeness score tool. Such information include accurate description of adverse drug reaction, patient details and medicine information. Reports with complete information enables statistically valid assessment of data such as for signal generation.

The MCAZ is committed to provide causality assessment feedback to reporters. In this regard, reporters are encouraged to provide their contact details both postal and email addresses. In addition, contact details enable follow-up by the MCAZ for missing information or other clarifications related to the reported cases. Figure 1 below provides a cumulative summary of ICSRs that were received by the MCAZ for the period January to September 2017.

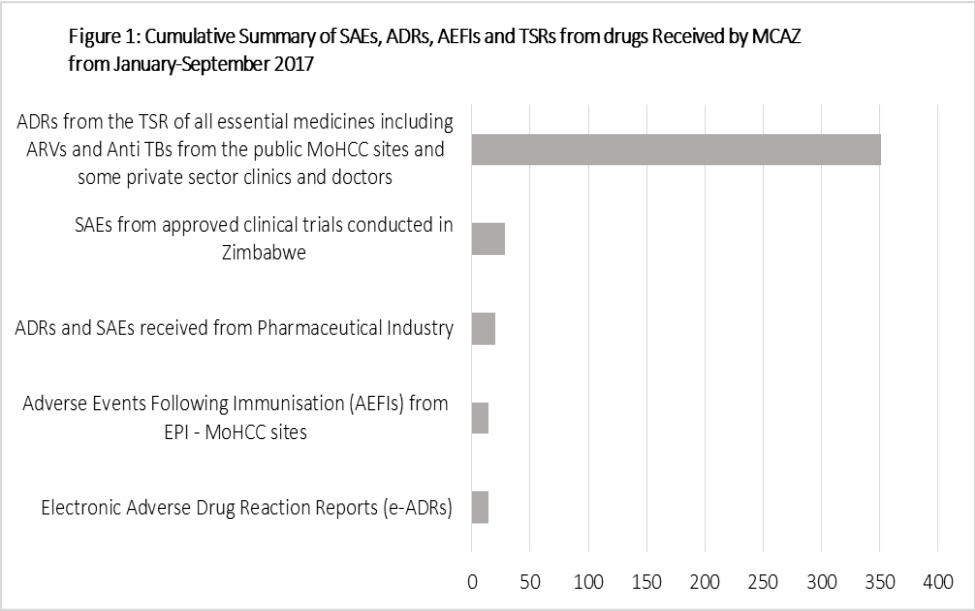

Figure 1: shows that a total of 427 Individual Case Safety Reports (ICSRs) were received during the period January to September 2017. The majority of these reports (82%) were ADRs from the TSR of ARVs and Anti TBs including all other essential medicines.

Electronic Adverse Drug Reaction Reporting (E-ADR)

This is a web based Individual Case Safety Report (ICSR) management system for pharmacovigilance online reporting. The MCAZ launched the e – ADR reporting platform in September 2016. This reporting platform can be used by patients, consumers, pharmaceutical industry, clinical trials and all other healthcare professionals. Clinical trials investigators are encouraged to provide details about patient initials or ID, MCAZ clinical trial reference number and/or acronym under additional information section. Information relating to patient age, date of adverse drug reaction onset, medicine start and stop dates is required and is regarded by the WHO – UMC as mandatory. Additional information section on the e – ADR reporting form can also be used to include laboratory test results, clinical trial information, such as causality assessment, clinical trial MCAZ reference/acronym.

5. NEW MCAZ REPORTING TOOLS

T. Nyengerai

Figure 2: Number of adverse drug reaction (electronic and non-electronic) reports received by the MCAZ and reporting provinces for the period January to September 2017.

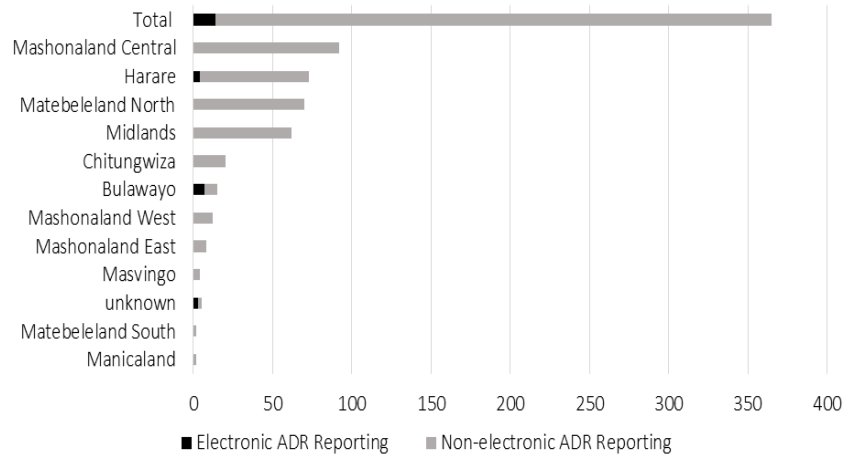

Figure 3: Comparison of electronic and non-electronic ADR reports received by the MCAZ for the period January to September 2017

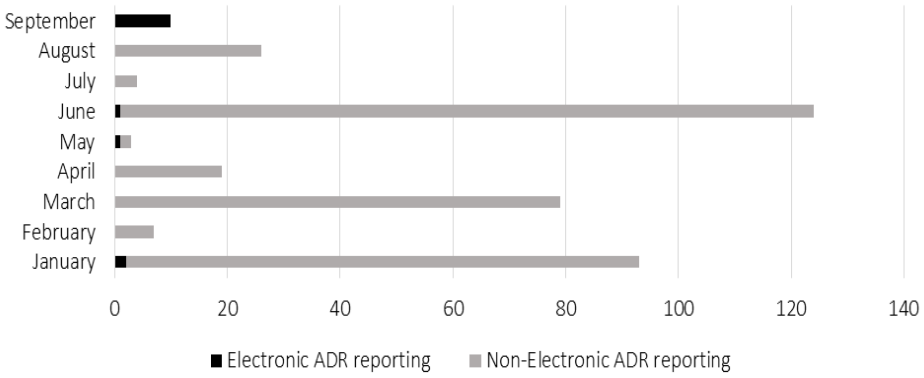

Figure 2 and 3above compare electronic and non-electronic ADR reports received by the MCAZ from January to September 2017. Non-electronic ADR reports as presented in Figure 2 and 3 refers to adverse drug reaction reports that were received by the MCAZ using paper ADR forms. The graph indicates that currently the majority of healthcare professionals are using non-electronic ADR reporting method. The MCAZ encourages all healthcare professionals with internet facilities to try online electronic ADR reporting using the hyperlinks provided under reporting tools. Concession Hospital from Mashonaland Central reported the highest number of reports. Bulawayo City health reported the highest number of electronic ADR reports and these were mainly received from Njube Clinic.

CONCLUSION

The MCAZ appreciates the tremendous support from all healthcare professionals and patients in strengthening pharmacovigilance activities in Zimbabwe through their participation in reporting ADRs / AEs. All reporters are encouraged to continue reporting using the above mentioned reporting tools. However, for reporters with internet facilities, they are encouraged to try the online electronic ADR reporting. Reporters are also recommended to provide as much information as is possible for the purpose of good quality and statistically sound reports.

6. Pharmacovigilance Regional Centers

C.M Mututa, T. Nyengerai

Introduction

The Medicines Control Authority of Zimbabwe (MCAZ) in collaboration with the Ministry of Health and the Directorate of Pharmacy Services (DPS), has been running the Targeted Spontaneous Reporting of Essential Medicines (TSR) programme to monitor all ADR from ARVs, Anti-TB medication and other Essential Medicines. The program started in September in 2012 and the main objective was to strengthen pharmacovigilance activities in Zimbabwe. Healthcare professionals were trained over the years in areas relating to pharmacovigilance overview and functions, quality reporting of adverse drug reactions and feedback was also provided on all individual case safety reports statistics. Professionals that were trained include nurses, pharmacists, medical doctors and other health professionals.

MCAZ has been visiting public health care centres and conducting trainings workshops across all the 10 provinces with a goal of increasing awareness and knowledge of the various pharmacovigilance activities with a focus on the TSR program. As of December 2017, a total of 962 professionals had been trained and a total of 224 sites visited and sensitized on pharmacovigilance programs. Fig 1 below shows the distribution of healthcare professionals trained by the MCAZ:

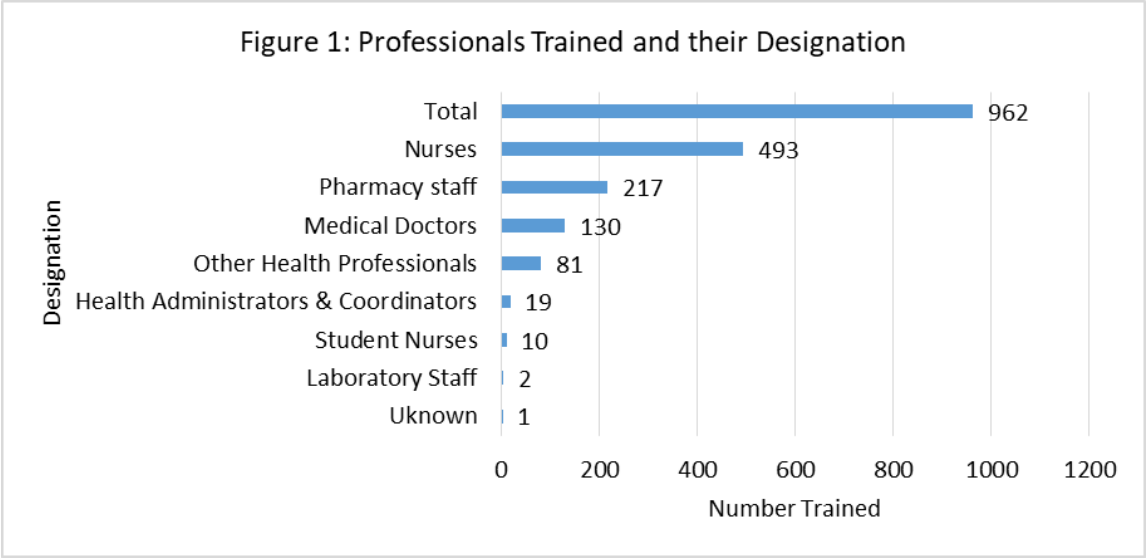

Figure 1 highlights that a total of 962 health professionals were trained across the 10 provinces during the period September 2012 to December 2017 on Targeted Spontaneous Reporting (TSR) of Adverse Drug Reactions. The bulk of trained healthcare professionals were nurses (51%) followed by pharmacy staff (23%).

The number of the trained professionals has been steadily increasing TSR programme as shown by Fig. 2 and 3 below. The figures also show that at least 10 sites have been sensitized and trained in each province. The MCAZ intends to carry on with this momentum in 2018 and visit more health care centres thereby increasing the awareness of the TSR programme and other pharmacovigilance activities.

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6. Pharmacovigilance Regional Centers

C.M Mututa, T. Nyengerai

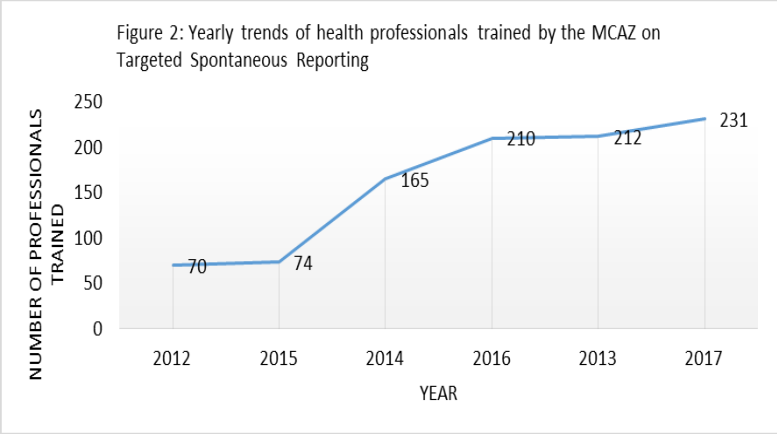

Fig. 2 : Yearly Trends of Health professionals trained by MCAZ

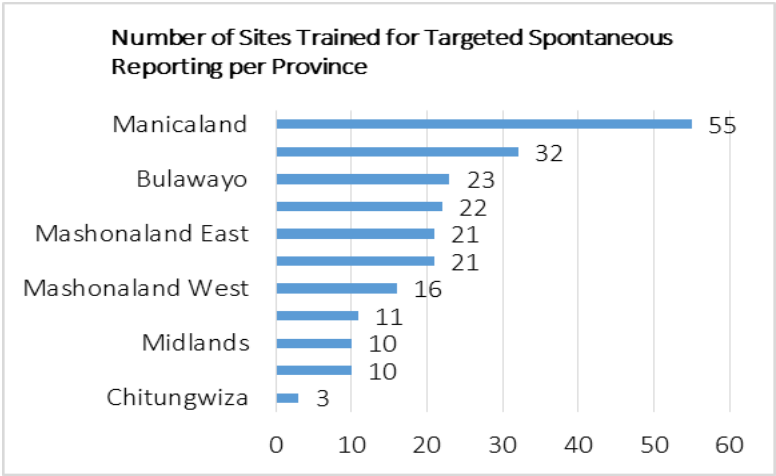

Fig. 3 Number of Sites visited per province by MCAZ

Setting of Pharmacovigilance Regional Centres

From the TSR programme, MCAZ has identified and consulted in all 10 provinces at provincial and district management levels including, Provincial Medical officers, Provincial nursing officers, Provincial Pharmacists, District Medical officers and District Nursing officers to set up regional pharmacovigilance centres in an effort to decentralize and improve the pharmacovigilance system in Zimbabwe. The guidelines for this programme have been drafted and will be circulated for review by all stakeholders that will be co-ordinating partners such as the Ministry of Health, AIDS and TB Unit and DPS. The program will be coordinated by the MCAZ as the National Pharmacovigilance centre and the DPS as the pharmacovigilance focal team. The formalization of the pharmacovigilance public health regional centres will be done for all provincial and district centres as the focal centres in respective provinces.

We look forward to setting up these regional pharmacovigilance centres in 2018!!!!

EDITORIAL NOTE

Dear Reader

We would like to thank you for taking interest in reading our first volume of the bulletin for 2018 and your continued support in reporting ADRs and AEFIs to the MCAZ National Pharmacovigilance Centre. We are excited to have published a manuscript from the TSR programme and we are hoping for more in the coming year. We cherish your reports and will continue the publication of the Information bulletin as one of the ways of disseminating Drug Safety information to Healthcare professionals. Please note that the reporting of a seemingly insignificant or common adverse reaction or side effect may help pinpoint a more widespread adverse effect or prescribing problem. If you have questions on any area of concern, please write to us on 106 Baines Avenue, Harare or call us on 708225/792165, Cell:0772145191-3.

THANK YOU FOR READING

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Medicines Control Authority of Zimbabwe