NATIONAL DRUG AUTHORITY

# PHARMACOVIGILANCE Bulletin

Safe Drugs Save Lives

**Volume: 19 Issue 1,** July- September, 2024


## We hosted the ISOP Africa chapter annual meeting

# Message from the Secretary to the Authority

Pharmacovigilance remains a cornerstone of our mission to ensure that medicines and medical products are safe for all. At NDA, we are steadfast in our commitment to effective drug safety monitoring, working tirelessly to uphold the highest standards in protecting public health.

None of this would be possible without you, our valued stakeholders. From healthcare professionals to patients, industry partners, and researchers, your active participation in reporting, collaborating, and sharing insights strengthens our collective ability to identify and mitigate risks. For this, we extend our heartfelt gratitude.

This quarterly bulletin is more than a publication; it is a platform for sharing knowledge, fostering dialogue, and completing the feedback loop between the agency and its stakeholders. With every issue, we aim to empower you with the information and updates needed to enhance safety practices across all levels of healthcare delivery.

It is with great enthusiasm that I welcome you to this term's bulletin. I hope you find its content both engaging and informative as we continue this vital work together.

Thank you for your unwavering support and commitment to pharmacovigilance.

I thank you,

**David Nahamya**
Secretary to the Authority

> "It is with great enthusiasm that I welcome you to this term's bulletin. I hope you find its content both engaging and informative as we continue this vital work together."

# Note from the director Product Safety

As we continue our journey in safeguarding patient safety, I want to take a moment to emphasize the critical importance of pharmacovigilance in our healthcare ecosystem. The timely detection, evaluation, and mitigation of risks associated with medicines depend on the collective efforts of all stakeholders. Each of you, whether a healthcare professional, patient, industry partner, or regulator plays a pivotal role in ensuring the safe use of medicines.

A special word of gratitude goes to our healthcare professionals and patients who report adverse reactions. Your vigilance and dedication are the cornerstones of our ability to respond swiftly to emerging safety concerns. Each report you submit brings us closer to our shared goal of preventing adverse patient experiences and improving therapeutic outcomes.

This quarterly bulletin is one of the ways we keep you informed and engaged in pharmacovigilance. It serves as a platform to share critical updates, discuss emerging safety issues, and disseminate learnings from our collective efforts. Through it, we aim to strengthen awareness, provide actionable insights, and foster a culture of safety in medicine use.

In this issue, we delve into several key topics:

Insights into menstrual disturbances linked to hormonal contraceptives: Understanding these reactions to improve patient counselling and care.

Risk of hypokalaemia with lipid amphotericin B: A timely reminder of the need for monitoring in at-risk patients.

Our first reports on anticancer drugs: A significant milestone reflecting our growing vigilance in this critical therapeutic area.

Lessons from the ISoP Annual Meeting: Held in July, this meeting brought together experts to share innovations and strategies for advancing pharmacovigilance practices globally.

World patient safety day commemorations activities.

Your ongoing commitment and collaboration are the driving force behind our success in pharmacovigilance. Let us continue to work together to make medicines safer for everyone.

Thank you for your support, and I hope you find this bulletin insightful and engaging.

Warm regards,

**Dr. Helen Byomire Ndagije**

Director Product Safety

Volume: 19 Issue 1, July– September ,2024

# Editorial team



# IN THIS ISSUE

# LOCAL SAFETY INFORMATION

## Menstrual cycle and bleeding disorders with hormonal contraceptives

The jury continues to be set on benefits of hormonal contraceptives and their several known and potential risks. Among such risks as thromboembolic disorders, menstrual disorders have been documented to affect uptake and contribute to discontinuation of contraceptives among women. The national pharmacovigilance center at NDA has continued to receive an increasing number of cases related to menstrual cycle and bleeding disorders with these products and although this is a known adverse effect, we present a brief discussion on the current safety information in the hope of driving some risk minimisation actions for better patient experiences.

### Current reporting trends

We have received 732 reports on hormonal contraceptives (in the period 2011 – 30th September 2024), with 427 of these related to menstrual cycle and bleeding disorders (346 reported between 2023 and 2024) among women 18-44 years. The injectable and implant progestogens (etonorgestrel, levonorgestrel and medroxy progesterone) contributed to 60% of the bleeding cases. Bleeding disorders manifested as either heavy bleeding (37%), irregular intermenstrual breakthrough bleeding (40%) and the rest as absence or missed menses. Most cases were noted to be taking ethinyl estradiol with these progestogens and 8 cases were on dolutegravir based regimens. Average time to onset of the bleeding reactions was 2 months with some cases reporting occurrence even after 1 year. globally, 429 771 cases have been reported in the same period, and these demonstrate similar characteristics to the local reports. Half of the reports were against Covid 19 vaccines, 17% with levonorgestrel (12%), etonogestrel (4%) and medroxy progesterone (1.7%). Half of these reports (58.2%) were cases of irregular intermenstrual breakthrough bleeding, 25% were heavy bleeding and the rest were absent or missed menses.

### Information and guidance from the manufacturer

Manufacturers state that women are likely to have changes in their menstrual bleeding pattern which are unpredictable beforehand. These may include the occurrence of an irregular bleeding pattern (absent, less frequent, more frequent or continuous), and changes in bleeding intensity (reduced or increased) or duration. During clinical trial studies, Amenorrhoea was also reported in about 1 of 5 women while another 1 of 5 women reported frequent and/or prolonged bleeding. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Information, counselling and the use of a bleeding diary can improve the woman's acceptance of a bleeding pattern.

# Menstrual cycle and bleeding disorders with hormonal contraceptives continued...

Evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynaecological pathology or pregnancy.

### Insights from literature

Literature shows that long-acting progestogen -only hormonal contraceptives injections are associated with highest risk of disturbances, followed by implants, IUDs and oral pills having least bleeding disturbances. Long-acting progestogen-only hormonal contraceptives like levonorgestrel subdermal implants caused 75 to 80% of women to have irregularities in bleeding pattern (mostly delayed or intermenstrual bleeding) during the first year of use. This improved with prolonged use but half of the users still had irregularities after 4 years. Injectable progestogens showed disturbances in 80% of users, but unlike implants, this did not improve with prolonged use. Combined monthly estrogen-progestogen injections had better menstrual cycle control with half of the users having normal cycles in the first year of use. Combined hormonal oral pills had 90% of users with normal cycles while IUDs had 20% of users with uncontrolled cycles in the first 3 months which improved with prolonged use.

### Final take

It's clear that menstrual cycle and bleeding disorders are an existential drawback associated with hormonal contraceptives. As we continue to document these cases, and analyse them for more insights, we encourage all health care professionals to provide the requisite support (manage symptoms and other diagnostic checks), information (on risk of disorders) and guidance (on what to do including maintenance of menstrual diaries) to users to ensure better patient experiences.

*1. S. Datey, L.N. Gaur, B.N. Saxena,Vaginal bleeding patterns of women using different contraceptive methods (implants, injectables, IUDs, oral pills)—An Indian experience: An ICMR task force study,Contraception,Volume 51, Issue 3,*

# Partial blindness with Amphotericin B

A 43-year-old male previously managed for aspergillosis with Amphotericin deoxycolate in 2023 experienced blindness. When the patient was re-challenged with liposomal Amphotericin, he still complained of partial blindness. Upon further investigation, the patient noted that the nurses were not hydrating him with normal saline before administration.

The drug was withdrawn and the patient was recovering with sequelae by the time of reporting.

Though rare, there have been documented cases where patients experienced acute visual loss after receiving amphotericin B with risk factors such as electrolyte imbalance, higher cumulative doses of Amphotericin B,

Volume: 19 Issue 1, July– September ,2024

# Partial blindness with Amphotericin B continued...

longer treatment duration, pre-existing renal impairment and the potential for ocular toxicity with amphotericin B particularly in patients with pre-existing conditions affecting

Prompt recognition and management of any visual disturbances due to Amphotericin B administration are essential to mitigate long-term consequences such as complete blind-

# Chemotherapy-Associated Adverse Drug Reactions

This section presents an analysis of ADRs observed in four patients undergoing chemotherapy for various cancers. The common reactions identified included dizziness, headaches, itching, swelling, numbness, and paresthesia. Although these symptoms were concerning, all patients reported recovery or resolution of their symptoms over time with ongoing treatment. Below is a detailed evaluation of the ADRs in each case and their potential relationship to the medications used, along with recommendations based on the manufacturer's Summary of Product Characteristics (SmPCs).

The first case involves a 74-year-old male patient, K.Y., with oesophageal cancer. He experienced dizziness, blurred vision, and headaches following chemotherapy. His treatment regimen included Paclitaxel, Carboplatin, Dexamethasone, Metoclopramide, and Ondansetron. These symptoms are consistent with the known ADRs of Paclitaxel and Carboplatin, which are associated with neurotoxicity and visual disturbances.

Dexamethasone may also contribute to headaches and visual symptoms. According to the SmPCs for Paclitaxel and Carboplatin, monitoring for neurotoxicity and managing symptoms accordingly is recommended. For visual disturbances, dose adjustments may be necessary. The SmPC for Dexamethasone advises monitoring for headaches and managing them as appropriate.

The second case involves a 65-year-old male patient, M.J., with prostate cancer. He developed itching and swelling of the legs three months after chemotherapy. His medications included Zolendronic acid, Docetaxel, Ondansetron, and Metoclopramide. Itching and swelling are recognized side effects of Docetaxel, which can cause fluid retention and dermatologic reactions. Zolendronic acid may also cause skin-related ADRs. The SmPC for Docetaxel advises monitoring for signs of fluid retention and managing dermatologic reactions with appropriate interventions, such as dose adjustments. For Zolendronic acid, the SmPC recommends monitoring for skin reactions and considering alternative bisphosphonates in cases of severe reactions.

# Chemotherapy-Associated Adverse Drug Reactions continued...

The third case involves a 63-year-old male patient, T.S., with pancreatic cancer. He reported dizziness during chemotherapy. His treatment included Cisplatin and Magnesium sulfate. Cisplatin is known to cause neurotoxicity, leading to dizziness. Magnesium sulfate, used to prevent Cisplatin-induced hypomagnesemia, may also contribute to electrolyte imbalances, exacerbating the dizziness. According to the Cisplatin SmPC, monitoring for neurotoxicity is recommended, and dizziness should be managed through dose adjustments or treatment pauses. Magnesium levels should be regularly monitored, with electrolyte imbalances corrected according to clinical guidelines.

The fourth case involves a 54-year-old male patient, N.M., with colon cancer. He experienced numbness and paresthesia after chemotherapy. His regimen included Oxaliplatin and 5-Fluorouracil. These symptoms are characteristic of Oxaliplatin-induced peripheral neuropathy, a well-known neurotoxic effect that can be dose-dependent and persistent. The Oxaliplatin SmPC highlights the need to monitor for peripheral neuropathy and suggests dose adjustments or discontinuation if the con-dition becomes severe. Symptom management strategies, such as using supple-ments or medications like pregabalin or gabapentin, are also recommended in the SmPC.

# SAFETY ALERTS FROM OTHER COUNTRIES

## Amphotericin B (lipid formulations)

## Risk of hyperkalaemia

**Europe:** The PRAC of the EMA has recommended updating the product information for amphotericin B (lipid formulations, AmBisome® and Abelcet®) to include the risk of hyperkalaemia. PRAC has also agreed that no further action is deemed warranted at this stage for non-lipid amphotericin B (Fungizone®), of which product information already includes the risk of hyperkalaemia.

Amphotericin B is an antifungal medication used for serious fungal infections and leishmaniasis. Lipid formulations and non-lipid amphotericin B products are not equivalent in terms of pharmacodynamics, pharmacokinetics and dosing and so the products should not be used interchangeably without accounting for these diffences.

*The updated product information for lipid formulations of amphotericin B states:*

*"Cases of hyperkalemia (some of them leading to cardiac arrhythmias and cardiac arrest) have been reported. Most of them occurred in patients with renal impairment, and some cases after potassium supplementation in patients with previous hypokalemia.*

*Therefore, renal function and laboratory evaluation of potassium should be measured before and during treatment. This is particularly important in patients with pre-existing renal disease, who have already experienced renal failure, or in patients receiving concomitant nephrotoxic medications".*

**Reference:** PRAC recommendations on signals, EMA, 5 February 2024 (link to the source within

## 17-hydroxyprogesteronecaproate (17-OHPC)

## Suspension of marketing authorisations

**Europe:** The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended the suspension of the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC).

17-OHPC is a synthetic progestogen (steroid hormone that acts like progesterone). In some EU countries, 17-OHPC medicines are authorised as injections to prevent pregnancy loss or premature birth in pregnant women. They are also authorised for the treatment of various gynaecological and fertility disorders, including disorders caused by a lack of progesterone.

The PRAC reviewed the results of a large population-based study, which looked at the risk of cancer in people who had been exposed to 17-OHPC in the womb, over a period of about 50 years from the time they were born. Data from this study suggest that these people might have an increased risk of cancer compared with those who were not exposed to the medicines. These are summarised below;

**A.** The results of a large epidemiological study suggest an increased risk of

cancer in offspring exposed to 17-hydroxyprogesterone caproate (17-OHPC) in

utero. This risk is possible but cannot be confirmed due to study limitations.

**B.** A multicenter, double-blind randomised controlled trial has shown lack of

efficacy of 17-OHPC in the prevention of preterm birth. There is limited data of

efficacy in other obstetrical and gynaecological indications for which 17-OHPC

is authorised.

**C.** The benefit-risk balance of 17-OHPC-containing medicines is no longer

considered positive in all indications and therefore the marketing

authorisations of these medicines have been suspended in the European Union

(EU).

**D.** 17-OHPC-containing medicines should no longer be prescribed or dispensed. Alternative treatment options should be considered for all indications.

In view of the concern raised by the possible risk of cancer in people exposed to 17-OHPC in the womb, together with the data on the effectiveness of 17-OHPC in its authorised uses, the PRAC considered that the benefits of 17-OHPC do not outweigh its risks in any authorised use. The Committee is therefore recommending the suspension of the marketing authorisations for these medicines. Alternative treatment options are available.

**Reference:** *Patients and carers, EMA, 17 May 2024 (link to the source within www.ema.europa.eu)*

*(See also WHO pharmaceuticals newsletter No.4, 2023: Potential risk of cancer in people exposed in the womb and lack of effectiveness in Europe; US FDA news release on 6 April 2023: FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena, hydroxyprogesterone caproate injection (the same substance as 17-OHPC)*

# WE HOSTED THE INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE (ISOP) AFRICA CHAPTER MEETING

The International Society of Pharmacovigilance (ISoP) Africa Chapter brought its members together in a face-to-face meeting to network, share knowledge and ideas on current issues that are pertinent to the development of pharmacovigilance within the continent. The meeting was themed "Advancing Pharmacovigilance Practice in Africa: Moving from Data Collection to Data-Driven Decision Making."

The ISoP Africa chapter conference was held successfully in Kampala, Uganda at Speke Resort Munyonyo. The event attracted approximately 300 participants from 16 countries. There were 50 facilitators across 8 thematic sessions and over 25 poster presentations.

The Guest of Honor was the Hon Minister of Health Uganda, Dr Jane Ruth Acheng.

During the 3-day meeting, a wealth of knowledge, experiences, best practices and challenges faced in the field of Pharmacovigilance were shared. In addition, solutions were devised for moving forward to attain the vision of the ISoP Africa chapter which is to have a capacitated and coordinated pharmacovigilance pool of experts who collectively and harmoniously work together to advance the safety of patients in Africa

Throughout the meeting, the strength of collaboration was emphasized, and how the contribution in terms of expertise and time of each person could significantly increase the impact and practice of pharmacovigilance on the continent. Below are key challenges facing Pharmacovigilance that were commonly stated throughout the different themes along with possible solutions to address them.

**Key PV Challenges highlighted throughout the meeting**

Throughout our discussions, we've identified several key areas for improvement in pharmacovigilance (PV):

1. Developing better mechanisms for sharing data among different stakeholders who operate parallel PV systems.

2. Increasing reporting rates to ensure a more representative contribution of PV data from our region.

3. Investing in frameworks, resources, and expertise to effectively leverage emerging technologies like AI and machine learning.

4. Strengthening pharmacovigilance expertise and expert networks.

5. Emphasizing a patient-centered approach alongside existing efforts to ensure medicine quality and safety.

6. Working towards harmonized regulatory systems across the continent.

**Possible solutions to overcome these challenges**

Collaboration and data sharing were essential in ensuring that the appropriate stakeholders had access to the information needed to take necessary policy and regulatory actions. This allowed for the sharing of resources and expertise to advance the Pharmacovigilance agenda.

A continental approach that involved pooling country resources to strengthen systems collectively and allowed countries to grow together. The Smart Safety Surveillance program, piloted in different countries, was called "SMART" because they utilized available resources and reinforced existing systems. This system was effective because it relied on principles of data sharing and resource sharing, rather than creating parallel systems.

We learned how to leverage the already established VigiBase which is the largest safety database for signal detection. Additionally, we gained insights from the Pharmacovigilance system in Eritrea, where the country successfully used VigiBase for signal detection.

Leveraging on technical development partners; is one of the drivers of success in the AU-3S program where there is support from the MHRA, WHO and US-FDA.

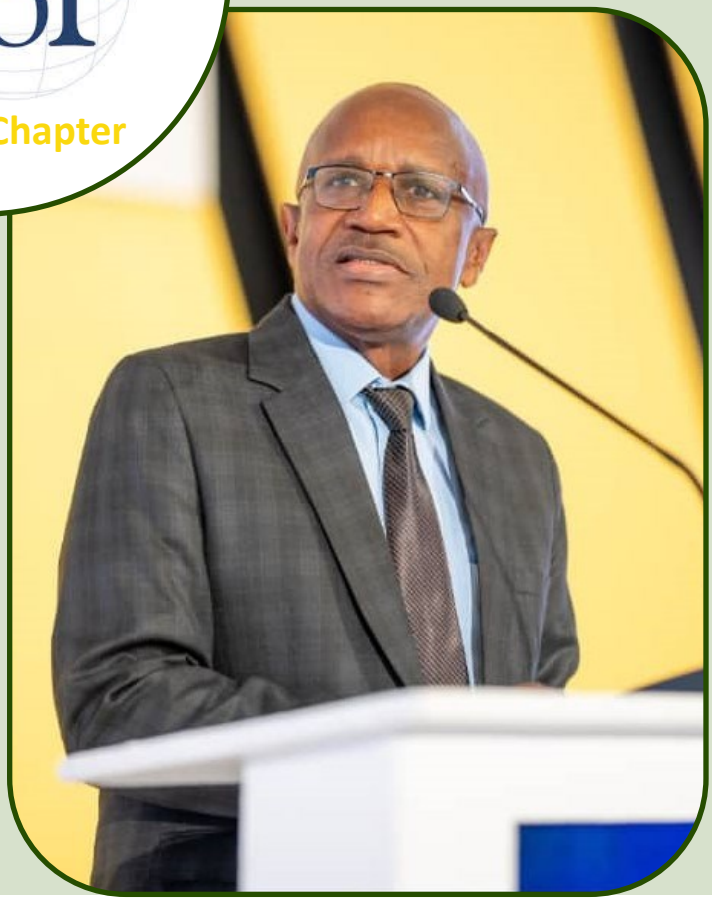
The role of patient reporting in pharmacovigilance was also highlighted as a successful strategy to increase reporting based on a study conducted in Uganda. From the patient reporting 9% of serious adverse events were identified. There is a need however to overcome challenges like the lack of precision, subjectivity and very large volumes of data.

The need for a patient-centered approach to Pharmacovigilance and the role of physicians/medical officers in reinforcing regulatory review and response of adverse events was highlighted. This strategy had been successful in Eritrea.

Volume: 19 Issue 1, July– September ,2024

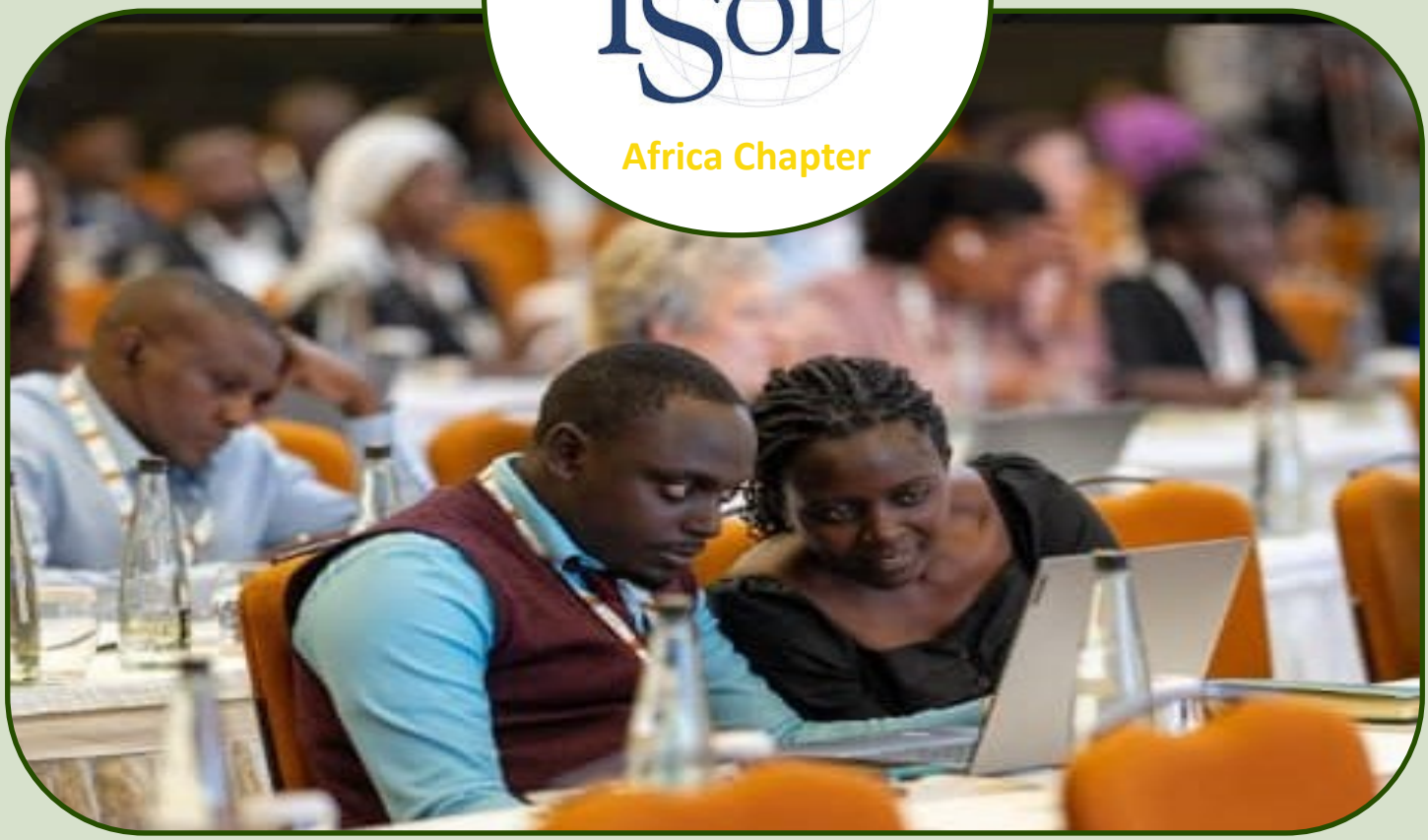


ISoP
Africa Chapter

Volume: 19 Issue 1, July– September ,2024


ISoP
Africa Chapter



# WORLD PATIENT SAFETY DAY COMMEMORATION ACTIVITIES

World Patient Safety Day is an opportunity to raise public awareness and foster collaboration between patients, health workers, policymakers and health care leaders to improve patient safety

World Patient Safety Day 2024 was observed on 27th September under the theme "Improving diagnosis for patient safety", with the slogan “get it right make it safe!” highlighting the critical importance of correct and timely diagnosis in ensuring patient safety and improving health outcomes.The main event was held at Wakiso HC IV in Wakiso district. A diagnosis identifies a patient’s health problem, and is a key to accessing the care and treatment they need. A diagnostic error is the failure to establish a correct and timely explanation of a patient’s health problem, which can include delayed, incorrect, or missed diagnoses, or a failure to communicate that explanation to the patient. The objectives of this year’s commemorations were;

- To raise awareness of the role of patients in ensuring their safety while they receive care.
- To highlight the fact that diagnostic safety can be significantly improved by addressing the systems-based issues and cognitive factors that can lead to diagnostic errors. Systemic factors are organizational vulnerabilities that predispose to diagnostic errors, including communication failures between health workers or health workers and patients, heavy workloads, and ineffective teamwork. Cognitive factors involve clinician training and experience as well as predisposition to biases, fatigue and stress.

NDA was well represented throughout the week-long activities that ranged from sensitization where we carried out drug safety sensitization to the general public at Wakiso HC IV, and the health workers in a medical camp and the last day that involved a key note speech from the minister of health for state in charge of general duties. 128 T-shirts, 10 caps, 50 bulletins and two ADR booklets were also distributed to foster the drug safety monitoing message.

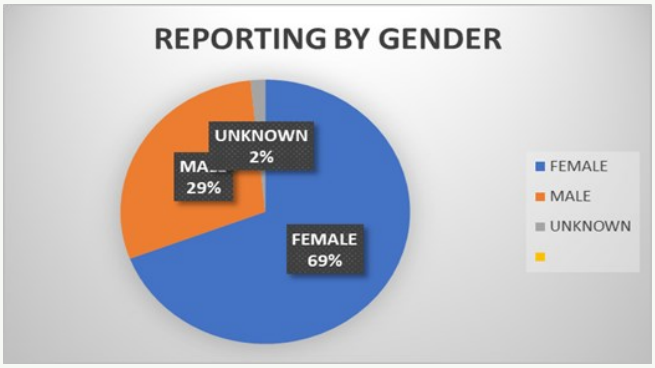

**LEFT:** Arrival of the state minister of health in charge of general duties, Hon Anifa Kawooya Bangirana

**RIGHT:** NDA representatives at the WPSD 2024

# ANALYSIS FOR Q1 FY 2024/25

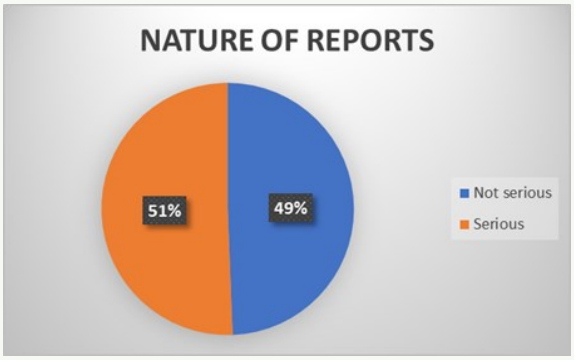
## Reporting by Gender

| Gender | Number of reports |
|---|---|
| FEMALE | 722 |
| MALE | 304 |
| UNKNOWN | 17 |
| Grand Total | 1043 |



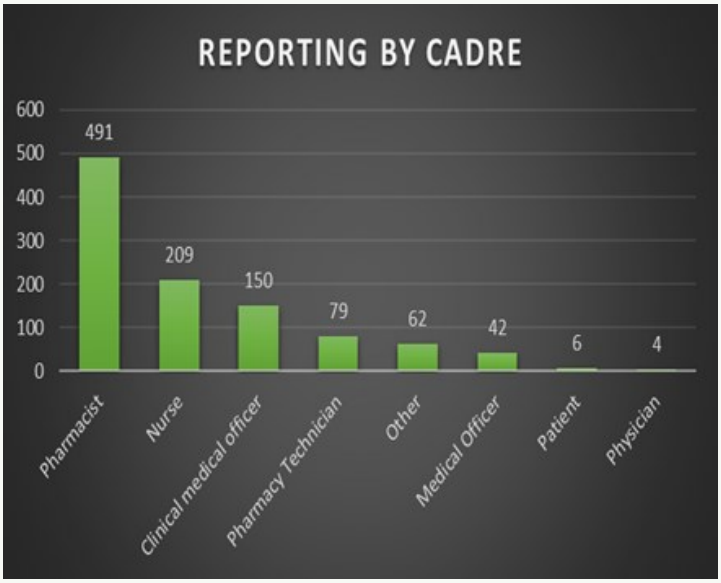

## Nature of reports

| Nature of reaction | Number of reports |
|---|---|
| Not serious | 515 |
| Serious | 528 |
| Grand Total | 1043 |




## Cadre

| Cadre | Number of reports |
|---|---|
| Pharmacist | 491 |
| Nurse | 209 |
| Clinical medical officer | 150 |
| Pharmacy Technician | 79 |
| Other | 62 |
| Medical Officer | 42 |
| Patient | 6 |
| Physician | 4 |
| Grand Total | 1043 |



# ANALYSIS FOR Q1 FY 2024/25

## Mode of reporting

| Channel | Number of reports |
|---|---|
| WhatsApp | 634 |
| Email | 155 |
| ADR form Physical | 102 |
| Online | 58 |
| Vigiflow | 55 |
| Mobile App | 39 |
| Grand Total | 1043 |
| | |

## Reporting by region

| Region | Number of reports |
|---|---|
| Central | 645 |
| Eastern | 108 |
| South West | 102 |
| Northern | 61 |
| West Nile | 50 |
| Western | 42 |
| South East | 35 |
| Grand Total | 1043 |

## Top 20 reported drugs

| Row Labels | Count of DOR |
|---|---|
| TDF/3TC/DTG | 193 |
| NIFEDIPINE | 75 |
| ETONOGESTREL | 64 |
| LEVONORGESTREL | 44 |
| TENOFOVIR | 41 |
| BENDROFLUMETHIAZIDE | 40 |
| DOLUTEGRAVIR | 35 |
| MEDROXYPROGESTERONE ACETATE | 28 |
| RIFAPENTINE/ISONIAZID | 27 |
| FUROSEMIDE | 23 |
| RHZE | 17 |
| AMLODIPINE | 17 |
| CEFTRIAXONE | 16 |
| SULFAMETHOXAZOLE/TRIMETHOPRIM. | 15 |
| PENTA VALENT | 14 |
| METFORMIN | 12 |
| LINEZOLID | 12 |
| CYCLOSERINE | 11 |
| NIRMATRAVIR/RITONAVIR | 11 |
| IUD | 11 |

## Top 20 Districts

| Districts | Number of reports |
|---|---|
| Wakiso | 202 |
| Kampala | 174 |
| Luweero | 173 |
| Mbarara | 56 |
| Butaleja | 46 |
| Arua | 41 |
| Lira | 40 |
| Mubende | 31 |
| Jinja | 28 |
| Gulu | 20 |
| Lyantonde | 20 |
| Masaka | 18 |
| Mbale | 16 |
| Kassanda | 14 |
| Hoima | 13 |
| Kayunga | 13 |
| Kabale | 12 |
| Masindi | 11 |
| Soroti | 10 |
| Bududa | 10 |

# ANALYSIS FOR Q1 FY 2024/25

## Top 20 facilities

| Facility | Number of reports |
|---|---|
| LUWEERO GENERAL HOSPITAL | 171 |
| ENTEBBE RRH | 114 |
| MUGABI MEDICAL CENTER | 79 |
| UGANDA HEART INSTITUTE | 60 |
| KIRUDDU NR HOSPITAL | 58 |
| MBARARA RRH | 46 |
| BUSOLWE GENERAL HOSPITAL | 43 |
| LIRA RRH | 40 |
| ARUA RRH | 39 |
| MUBENDE RRH | 30 |
| JINJA MAIN PRISON HC III | 25 |
| MULAGO NATIONAL REFERRAL | 22 |
| GULU RRH | 20 |
| LYANTONDE GENERAL HOSPITAL | 20 |
| MJAP MULAGO | 16 |
| MBALE RRH | 16 |
| KITOVU HOSPITAL | 14 |
| KAYUNGA RRH | 13 |
| HOIMA RRH | 13 |
| KABALE RRH | 12 |