National Drug Authority

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PHARMACOVIGILANCE Bulletin

Safe Drugs Save Lives

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Remarks from the Secretary to the Authority

Throughout this year, our vigilant monitoring and proactive assessment of adverse drug reactions have been instrumental in upholding the highest standards of pharmaceutical safety. The strategic partnerships have fortified our ability to swiftly detect and address potential risks, ensuring the well-being of patients remains our top priority. I take this opportunity to re-affirm our commitment to ensure the safety of all drugs in the health system.

As we continue to pursue this aspiration, I would like to express my sincere appreciation to our esteemed healthcare professionals, regulatory partners, and most importantly, the patients who have actively reported safety information to NDA. Their invaluable insights have enriched our understanding of drug safety, particularly in diverse and vulnerable populations.

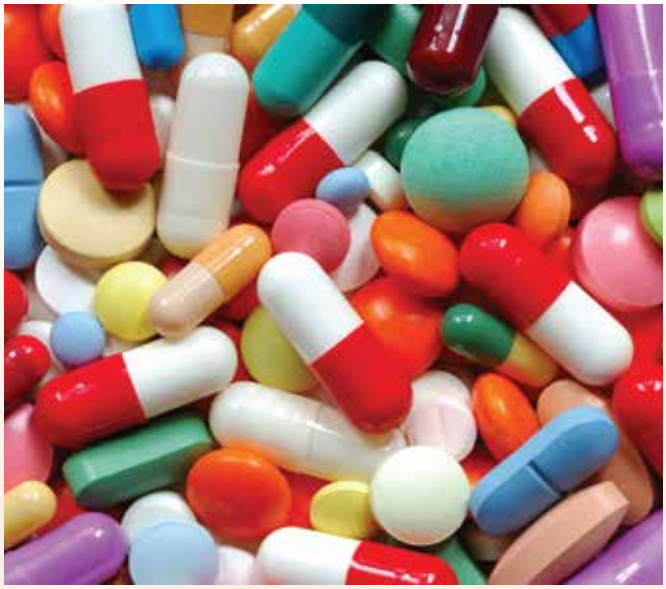
We remain resolute to our mission of protecting and promoting human and animal health, through strategic partnerships.

By fostering collaboration across the healthcare continuum, we aim to create a robust network that enhances our collective capacity to ensure the safety of pharmaceutical products. This commitment positions us for continued success in the dynamic field of pharmacovigilance.

As we embark on the new year 2024, let us carry forward the spirit of collaboration, innovation, and commitment to safeguarding the health of those we serve.

David Nahamya
Secretary to the Authority

Message from the Director Product Safety



Dear Esteemed Readers,

Our commitment to ensuring the safety and well-being of patients remains at the forefront of our endeavors. I am delighted to share some insights into the strides we have made in the realm of pharmacovigilance within the second quarter of FY 2023/24. In this edition of the Pharmacovigilance bulletin, we discuss; local and foreign safety label updates, a case of drug induced Toxic Epidermal Necrolysis (TEN), reporting of drug related defects, analysis of ADR reports, highlights of the PV stakeholders meeting and nationwide PV awareness campaign on mainstream media as well as insights on the country-wide distribution of PV IEC materials.

The Pharmacovigilance team at the National Pharmacovigilance Center (NPC) remains dedicated to monitoring and assessment of adverse drug reactions. The cornerstone of our efforts lies in the vigilant surveillance of pharmaceutical products, leveraging advanced technologies and collaborative partnerships to identify and address potential safety concerns promptly.

The invaluable perspectives shared by patients and healthcare providers contribute significantly to our understanding of drug safety dynamics, especially in diverse and vulnerable populations.

As we navigate the complexities of our field, let us remain dedicated to promoting patient safety in our different spheres of practice.

I want to take this opportunity to wish you a prosperous new year, 2024.

Dr. Helen Byomire Ndagije (PhD), FISoP
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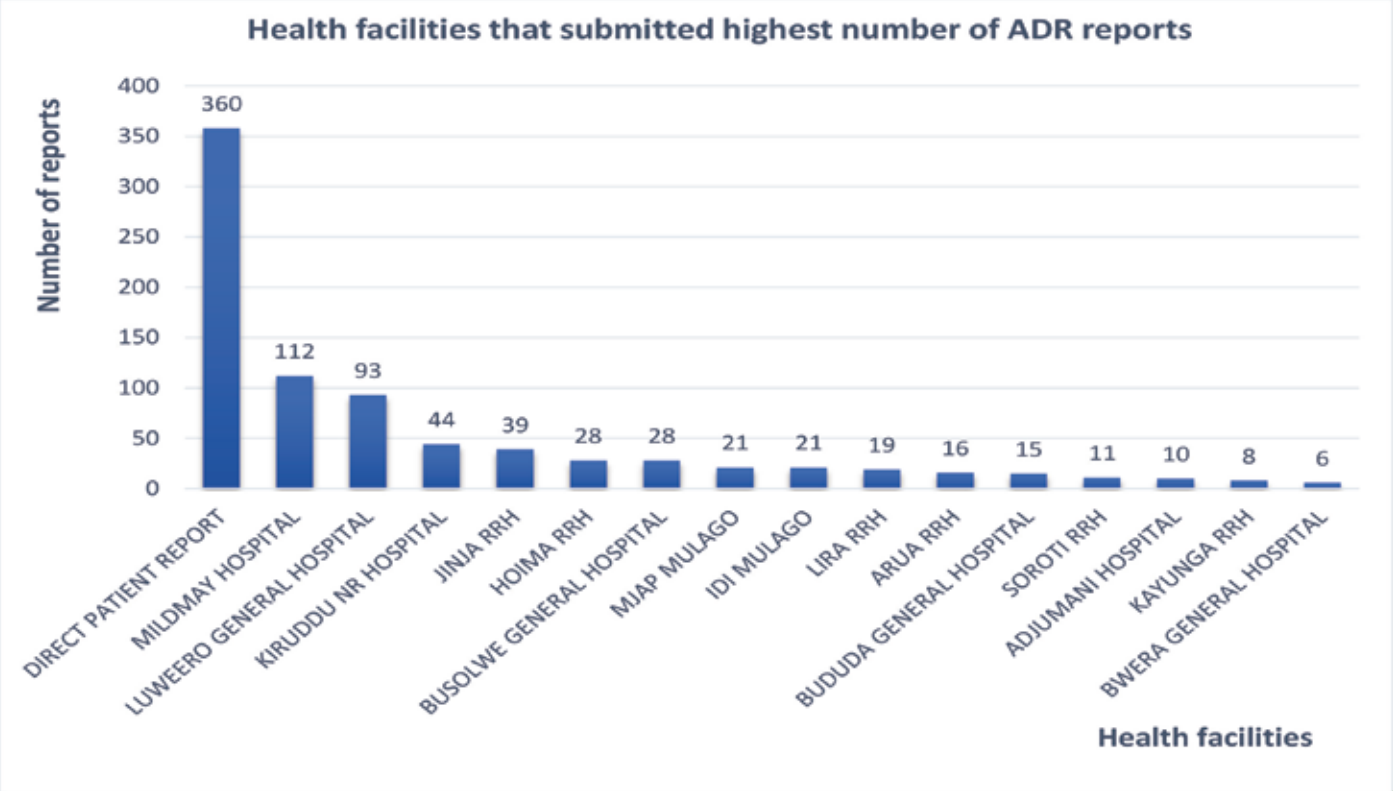
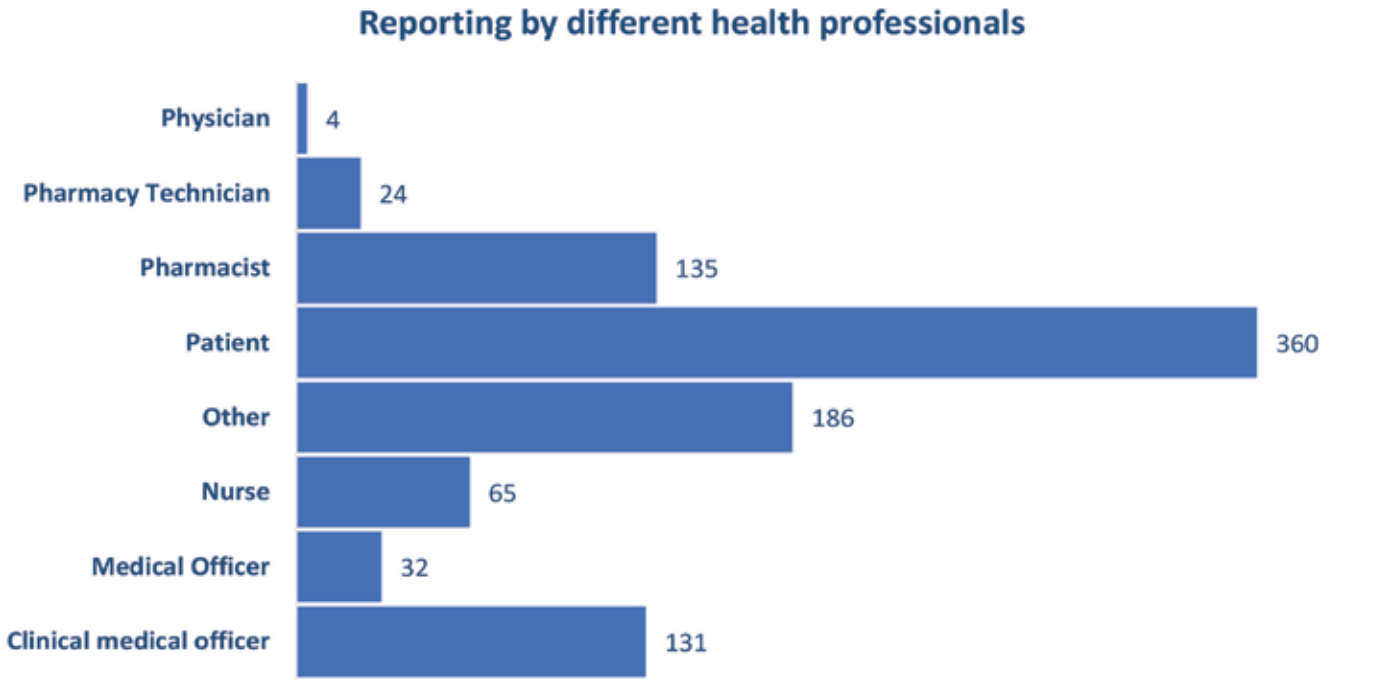
ANALYSIS OF ADR AND AEFI REPORTS RECEIVED FROM SEPTEMBER TO DECEMBER 2023

A total of 937 ADR/AEFI reports were submitted from the various sources to the National Pharmacovigilance Center (NPC) during the second quarter. Detailed analysis of these reports is provided hereunder:

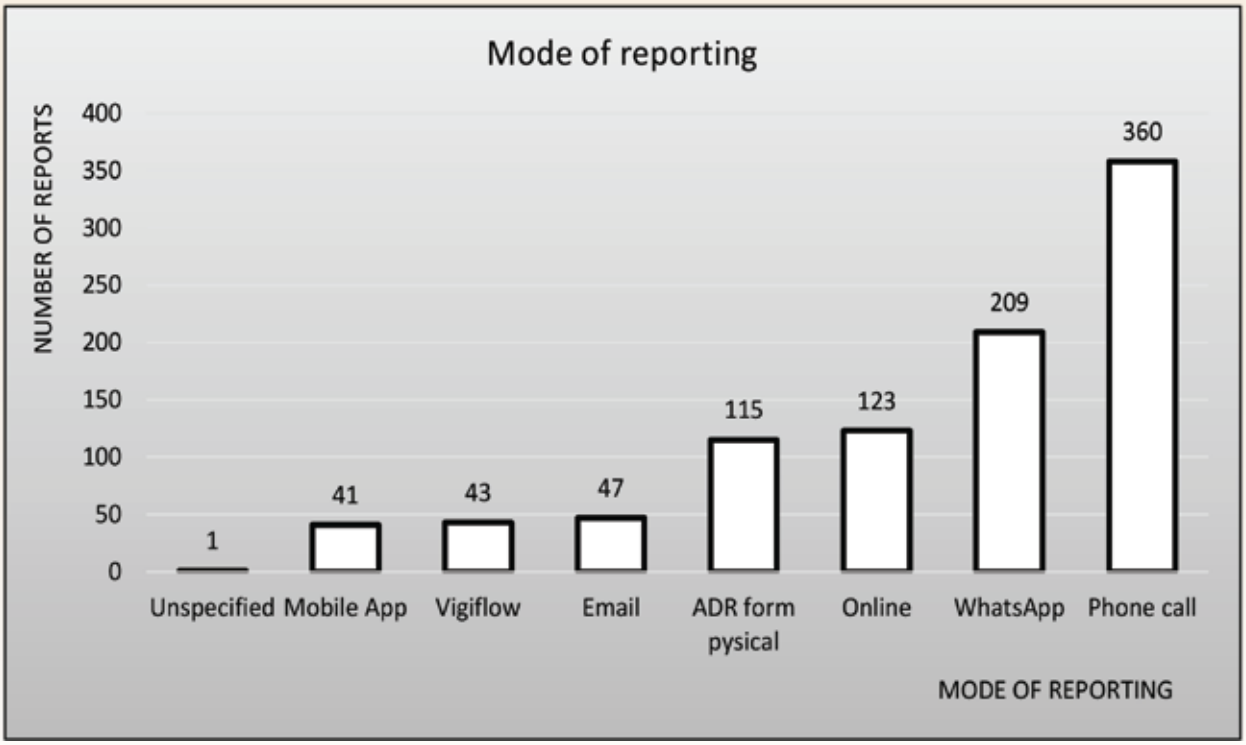
Most of the reports were submitted directly to the NPC by patients (n=360).



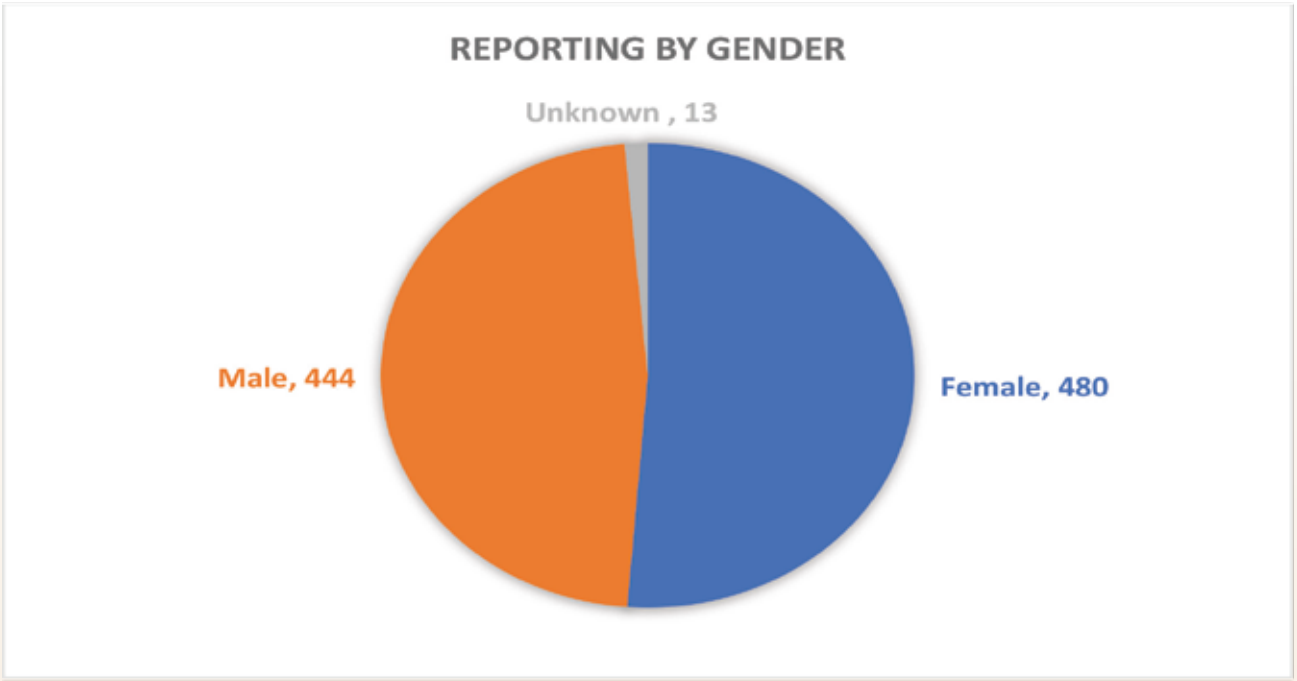
Among healthcare professionals, pharmacists (n=135) and medical clinical officers (n=131) submitted most of the reports. This was followed by the nursing cadre (n=65) and physicians submitted the least number of reports (n=4).



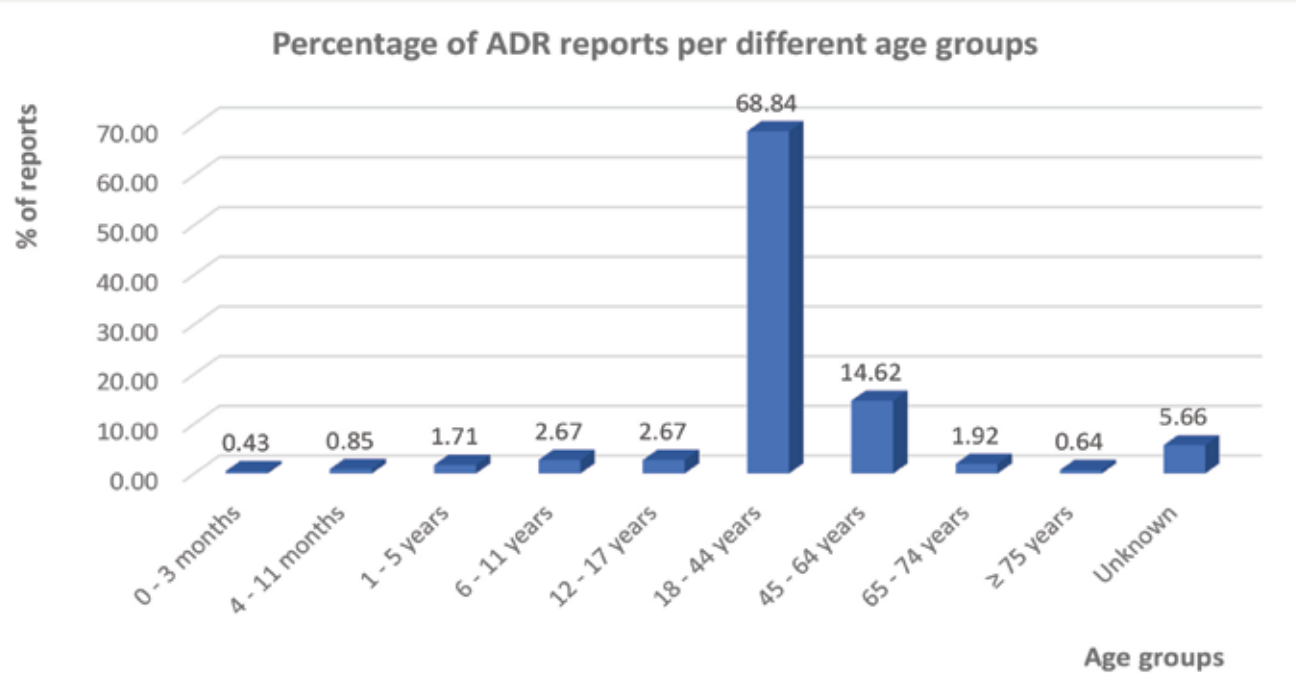
The reports from patients came in mainly through the phone call (n=360). The toll free line offered the best opportunity for patients to simply call in at any time and report about drug effects they experienced, this explains the high number of reports by patients through the phone call. However, quite a number of reports were submitted through the WhatsApp (n=209), online reporting (n=123) reporting platforms and the physical ADR reporting forms (n=115).



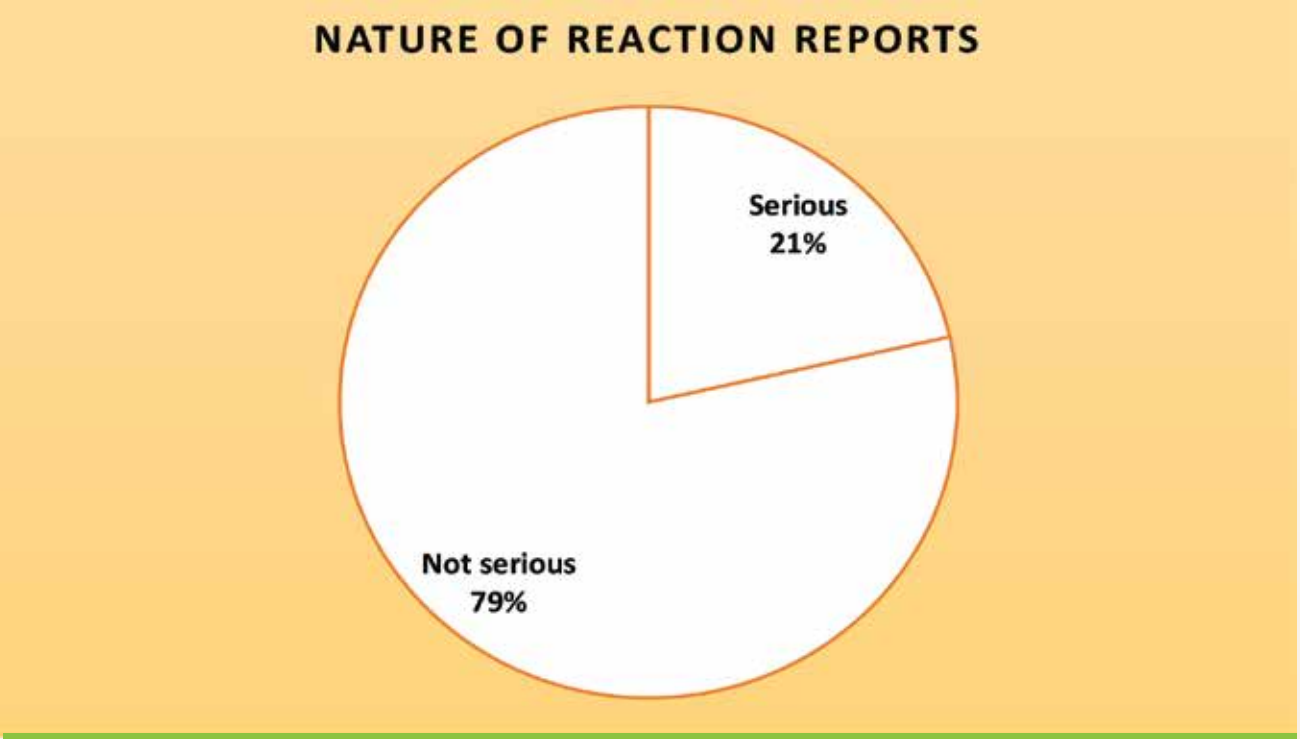
The ADR reports in both males and females were almost in equal proportions, with a few (n=13) unspecified genders. This trend deviates from previous quarters/terms where the reports among females have been consistently more. It's unclear what drivers influence trends in the gender characteristics of reports submitted.



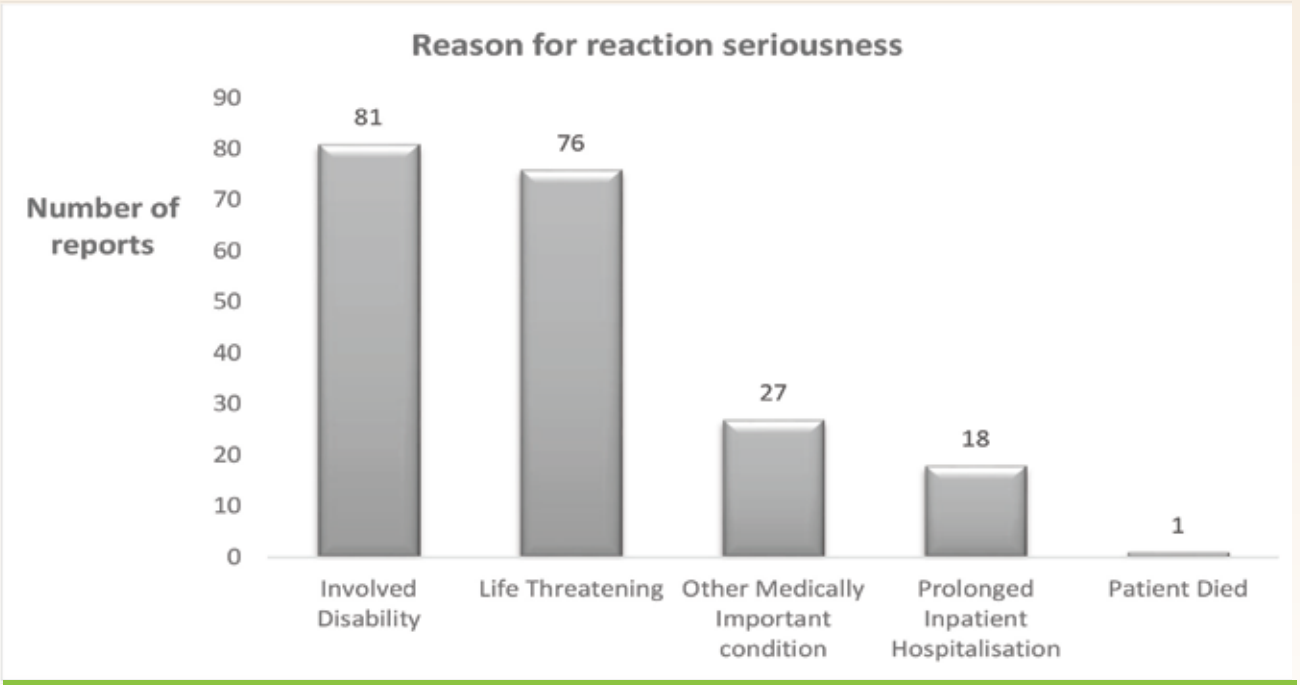
Analysis of the reports by the different age groups indicated that the reactions occurred mostly in adults of 18-44 years age group. This can be possibly explained by demographic age distribution of the country which consists mainly of this same age group and therefore gets more exposed to drugs compared to other age brackets.



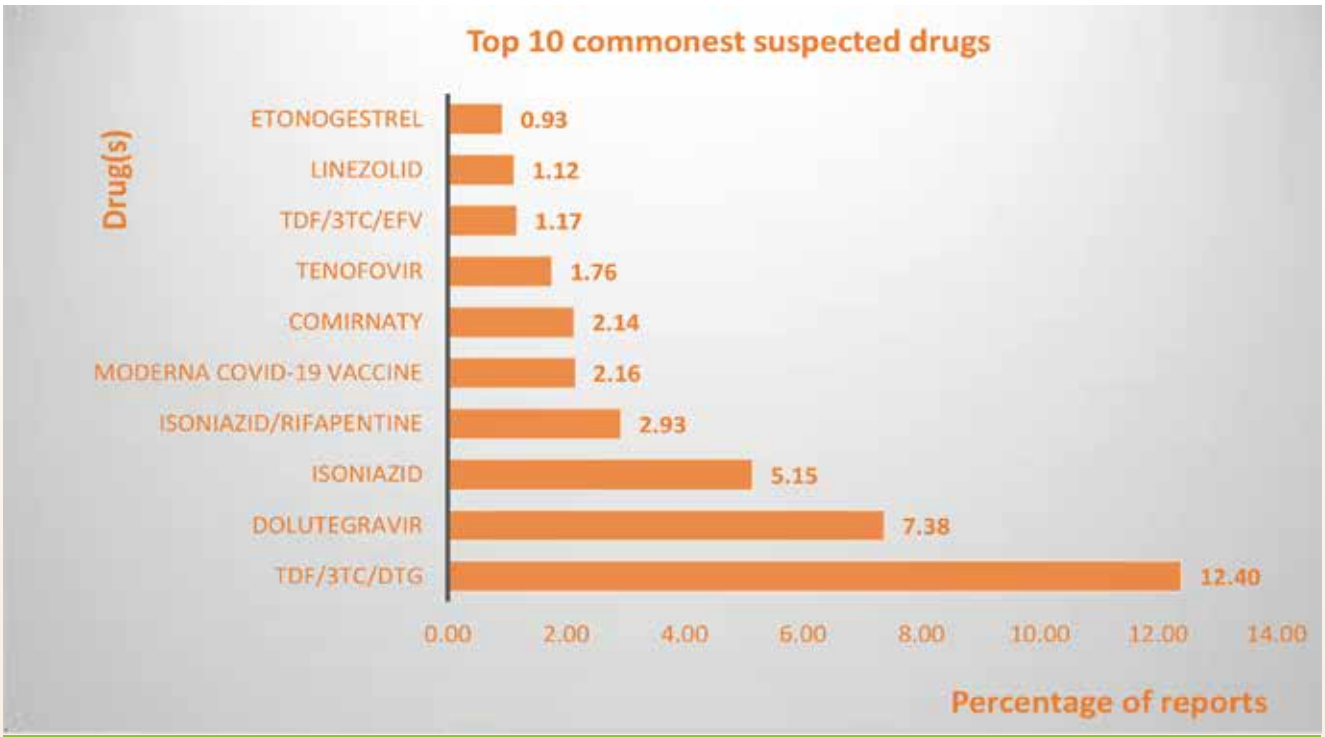
Majority of the reactions were not serious (n=79%). The serious reactions had various reasons for seriousness. A serious adverse drug reaction (serious ADR) is a noxious and unintended response to a drug that occurs at any dose and that; requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation/anomaly, results in persistent or significant disability or incapacity, is life-threatening, or results in death.



And of the serious ADR reports, majority were life threatening (n=76 and involved disability (n=81) Only one report involved death.



Overall, most reports were from HIV, TB and EPI drug products. DTG and its combination continued to be most reported against. This could be because all people living with HIV were transitioned to the DTG based regimen as first line drug leading to increased exposure.



The commonest reported reaction term was hyperglycemia (n=3.53%) as well as injection site pain (n=2.72%), headache (n=1.66%) and generalized body weakness (n=1.47%).

The high number of hyperglycemia reports correlates with the new characterized ADR of diabetes mellitus with DTG and the DTG based regimen. On the other hand, injection site pain, headache, general body weakness and fever are typical adverse vaccine related events following immunization (AEFIs) which can be attributed to the various ongoing vaccination campaigns

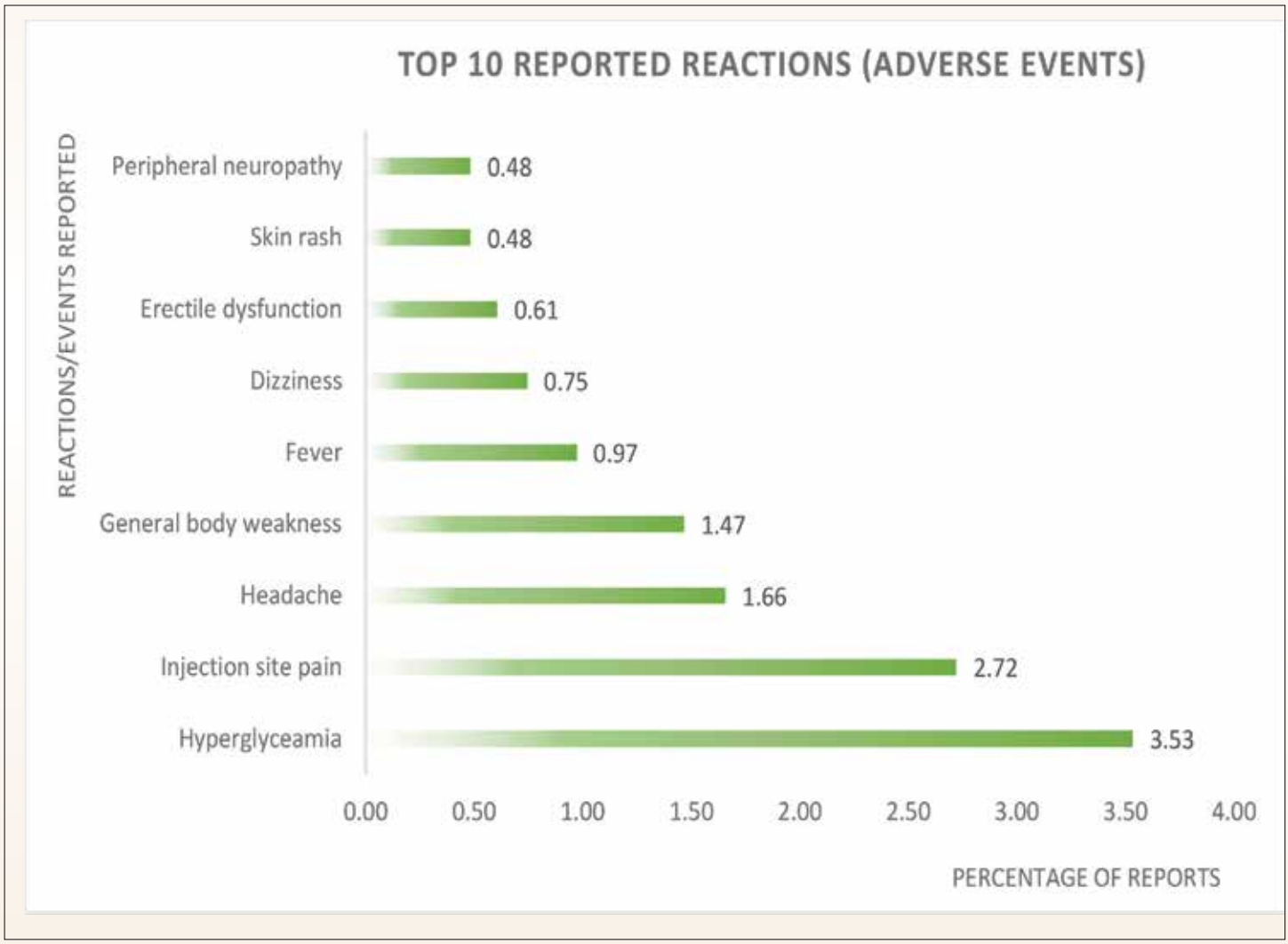


Figure 9: ***Most common reported preferred terms (reactions/events)***

ANNUAL PHARMACOVIGILANCE STAKEHOLDERS' MEETING

As is usually the case, the NPC annually organizes the Pharmacovigilance stakeholder's meeting to deliberate on important aspects of drug safety monitoring and devise ways of ensuring safety of the medicines on the market as well as well safe use of medicines. It is also during this meeting that the NPC communicates the milestones achieved and awards outstanding performance by the PV stakeholders in the ended previous FY.

This years' annual PV stakeholders' meeting was held on the 16th of November 2023, at the Imperial Royale hotel in Kampala, under the theme: "Harnessing strategic partnerships to promote drug safety in special populations". This theme was inspired by the fact that medicines safety monitoring is not prioritized in these very vulnerable but yet ignored population groups.

Expert physicians and researchers from the different scientific fields relating to the special groups delivered key note presentations and key panel discussions with emphasis on medication safety in the different special patient populations. These presentations were aimed at highlighting the safety priority and elicit interest of support from the various players. Four presentations were delivered to the stakeholders i.e. on medicine safety in pediatric, geriatric, pregnant and lactating mothers and vaccines safety.

During the same meeting, outstanding ADR reporters from the various health facility categories were recognized and awarded with tokens of appreciations. The meeting was attended by 132 stakeholders in total from different medical professions and health institutions. These included; pharmacists, Medical Doctors, Medical Clinical Officers, Nurses, Pharmacy Technicians, Hospital administrators and Directors, Pharmaceutical distributors etc. the occasion was graced by the permanent secretary of Ministry of Health as the guest of honor.

Photo showing panel discussions during the meeting: 1. Prof. Dan Kabonge Kaye (Obs/gyn), 2. Dr. Harriet Nankabirwa (Geriatrician), 3. Dr. Deogratius Munube (Pediatriacian) 4. Dr. Ombeva Malande (Vaccinologist & a Paediatric infectious diseases specialist

Figure 11: A group photo together with the guest of honor PS MOH (Dr. Diana Atwine), Secretary to the Authority, Director Product Safety and the participants

Figure 12: Dr. Harriet Nankabirwa delivering her presentation on pharmacovigilance in the geriatric population

Figure 13: Dr. Ombeva Malande presenting about vaccines safety monitoring and surveillance

Figure 15: Participants listening attentively during the meeting presentations

Figure 14: The Permanent Secretary of Ministry of Health, Dr. Diana Atwine together with the Secretary to the Authority (SA) presenting a plague and voucher to the top ADR reporter of FY 2022/23during the awards session as moderated by the manager PV

CASES OF INTEREST FROM LOCAL SAFETY INFORMATION

Case 1: Pyramax (Pyronaridine Tetraphosphate/Artesunate) Induced Toxic Epidermal Necrolysis (TEN)

Case narrative:

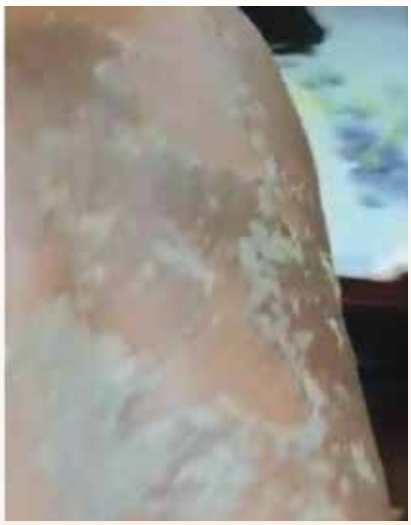
RS, a 43y/o female patient diagnosed with uncomplicated malaria following a positive MRT test result. She was given Pyramax 180mg/60mg (Pyronaridine tetraphosphate/Artesunate) 3 tablets OD for 3 days and Paracetamol tablets 1g TDS for 3 days.

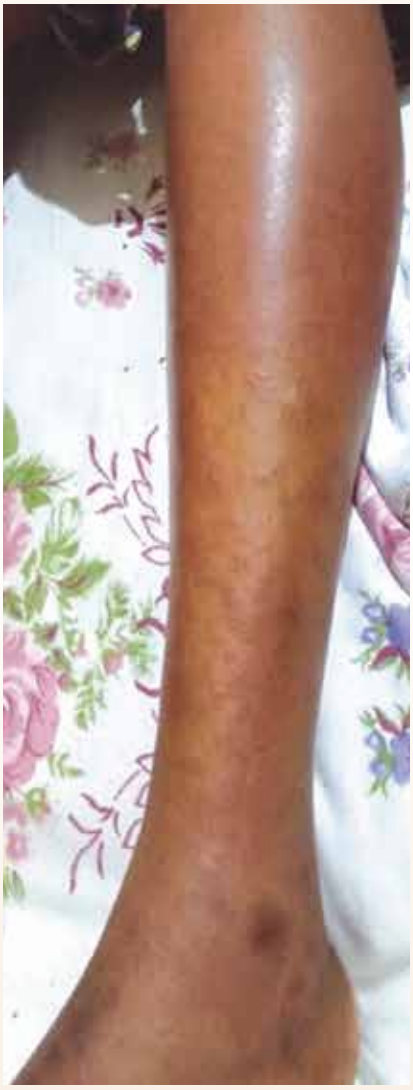
She had no complaint on day one of therapy, however, on day 3, she developed painful skin itching and rash which kept worsening days later. It was initially suspected to be measles and she was advised her to "take a lot of small fish (mukene/enkejje)".

The symptoms however kept worsening and this prompted her to consult a dermatologist who prescribed prednisolone, Panadol, amoxicillin, desloratadine, clobetasol fusidic B+, all for a period of 2 weeks.

The patient did not register any change but rather developed other worsening symptoms of "peeling of skin and swellings (edema) on the legs and hands, generalized itching and fever with difficulty to sleep".

Patient was not smoker and neither drinks alcohol. No further information was provided on reaction outcome.





Causality Assessment of the case:

The time of medication initiation and onset of event/reaction provides a plausible temporal association. There was a plausible relationship between nature of occurrence and prognosis of events (presenting symptoms) with the possible expected skin and subcutaneous tissue disorders of Pyronaridine tetraphosphate + Artesunate.

A causality assessment using Naranjo algorithm indicates a likely relationship between the events and the drugs used, with a score of +5.

Literature on the drug regimen administered (Pyronaridine tetraphosphate + Artesunate) provides a warning on possible hypersensitivity reaction under the "special warnings and precautions for use" section, which may include symptoms as experienced by RS in the case narrative above. No post market cases of Pyronaridine tetraphosphate + Artesunate induced skin hypersensitive reaction could be cited. However, the report missed some key information such as reaction outcome, family history regarding allergies associated with Pyronaridine tetraphosphate + Artesunate use and any other relevant laboratory tests conducted to rule out other alternative causes of the event or explain some of the symptoms such as edema. The above missing information is key for better assessment, characterization and understanding of the causal relationship between the event and the drugs used.

From the available information above, it can be deduced that the event/reaction was drug-induced and a hypersensitive skin reaction in nature, best described as Toxic Epidermal Necrolysis (TEN) associated with Pyronaridine tetraphosphate/Artesunate use.

Case discussion:

While TEN is not listed as one of the expected adverse effects or warnings in the Pyronaridine tetraphosphate/Artesunate SmPC, the presenting symptoms of rash, pruritus, blisters are expected as adverse events of Pyronaridine tetraphosphate/Artesunate. However, prognosis of the event rather suggests an allergic skin reaction.

TEN is an unpredictable, life-threatening drug reaction which results from extensive keratinocyte cell death leading to separation of significant areas of skin at the dermal-epidermal junction, with the production of bullae followed by skin sloughing. This extensive cell death also leads to mucous membrane detachment and contributes to the characteristic symptoms which include among others, blisters and large sheets of epidermis that slough off, leaving an exposed, weeping dermis.

While TEN is rare, with an incidence of 2 per million per year,1 it is a devastating condition, with a mortality rate of about 30%. Elderly patients and patients with extensive lesions have a higher mortality rate. Surviving patients completely heal in 3 to 4 weeks.

The exact mechanism of drug induced TEN still remains unknown. However, one theory holds that altered drug metabolism (e.g. failure to clear reactive metabolites) in some patients triggers a T-cell–mediated cytotoxic reaction to drug antigens in keratinocytes.

Equally, in the above case, the exact mechanism of Pyronaridine tetraphosphate/Artesunate induced TEN as described cannot be deduced. As per the SmPC, Pyronaridine tetraphosphate + Artesunate contains tartrazine (E102) and sunset yellow (E110) as colouring agents which may cause allergic reactions which may manifest as flushing, the appearance of wheals/urticarial.
Management of drug-induced TEN is dependent on the severity of the condition. Generally, withdrawal of the offending drug and management of the presenting symptoms with systemic or topical steroids suffices.

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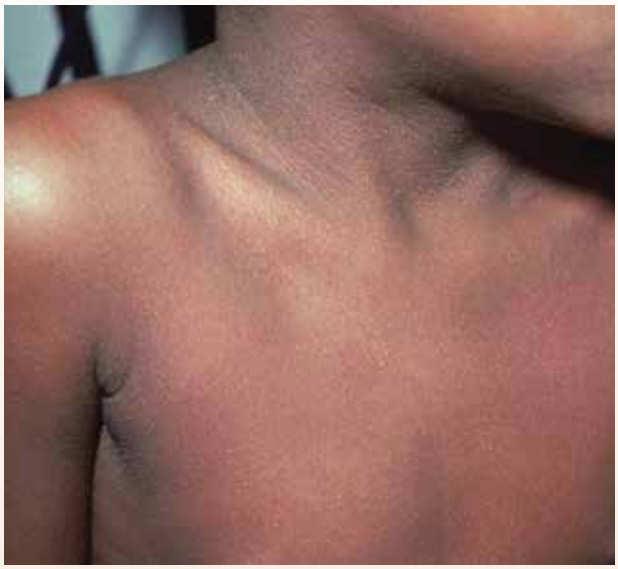
Case 2: PRURITIC SKIN RASH ASSOCIATED WITH CEFTRIAXONE

(Compiled by: GENZA Fulugensio, KONSUGI Paul, NAKIWALA Caroline & KIPROTICH Joshua)



Case narrative: K.J, an 8-year-old female weighing 15kg reported generalized body rash, itching, high fever(380C) and increased pulse rate (figure not specified) after receiving ceftriaxone 1g start dose. Ceftriaxone was withdrawn, patient given Hydrocortisone 100mg start, Paracetamol 500mg and tepid sponging leading to a positive outcome.

Causality assessment and case discussion

K.J developed generalized body rashes characterized with itching and from the report, these events started after administering ceftriaxone injection hence a plausible time-event relationship. Body rashes and itching are listed in the summary of product characteristics of ceftriaxone as possible adverse events.

A causality assessment using Naranjo algorithm indicated that the drug (Ceftriaxone) was probably associated with the events.

Known information about the case is not adequate to conclusively deduce that Ceftriaxone was the sole causative agent of the events. K.J still requires further evaluation for alternative causes of the observed adverse effects. More information regarding recent infections and laboratory tests including CBC and mRDT, family and drug use history would help to rule out any cases of existing allergies or establish the exact cause of the events but they were not provided.

Case discussion

Ceftriaxone is an antibiotic that belongs to a class of medicines known as cephalosporins. It's used to treat susceptible bacterial infections of the Lower Respiratory Tract, Skin and skin structure, bone and Joint, acute otitis media, UTI, septicemia, Pelvic inflammatory Disease, Intra-abdominal infections, meningitis, complicated gonorrhea and for surgical prophylaxis.

Some of the allergic reactions associated with ceftriaxone include itching, hives, body rashes and swelling of hands, face or mouth that arises after medicine administration.

Proposed mechanism of Ceftriaxone-induced rash has been failure of drug detoxification pathways leading to accumulation of harmful metabolites which in turn activate CD4 + and CD8 + T-cells. These cells release interleukin-5 which activates eosinophils and sets up an inflammatory cascade that results into the skin and subcutaneous tissue as described above.

It is advisable to first establish whether a patient is hypersensitive to ceftriaxone, cephalosporins or any other type of b-lactam agents. In case of severe hypersensitivity reactions, treatments with ceftriaxone must be discontinued immediately and adequate emergency measures initiated.

References

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The Critical Role of Consumer and Healthcare Professional Reporting in Detecting & Managing Drug-Related Defects

(Authors: Nasser Lubowa and Elijah Kirabira)

National Drug Authority implements various strategies to prevent, detect, and respond to the circulation of substandard and falsified medicines. Preventive measures include stringent border controls, inspection of medicine consignments, and licensing requirements for importing medications from certified manufacturers. For early detection, NDA utilizes rapid screening techniques like Mini-lab and regular testing of high-risk medications to assess quality. Once identified, substandard or falsified products are quarantined and withdrawn, followed by corrective measures or destruction.

Types of Drug-Related Complaints

Drug complaints can be categorized based on the defects in drugs or their impact on patients. These include adverse reactions, visible quality issues, and efficacy concerns. Globally, adverse drug reactions (ADRs) have been the primary focus, with significant advancements in their detection. These undesirable effects occur during normal treatment use. Voluntary reporting systems by HealthCare Professionals (HCPs), based on patient feedback during treatment or follow-up visits, facilitate early detection. Recently, direct patient reporting to National Regulatory Authorities(NRAs) has been encouraged for quicker identification of previously unnoticed ADRs. However, other drug-related complaints have not received comparable attention, despite their potential to cause harm.

Each drug form is prone to specific defects, rendering it unsuitable for the target population. For instance, public health products like gloves and condoms must be impermeable to ensure protection against infections.
Defects in tablets may include;

i. Chipping,
ii. Sticking,
iii. Color changes, or
iv. Odor development, among others.

Liquid medications might exhibit issues like;

i. Caking,
ii. Color changes,
iii. Foreign matter growth, or
iv. Visible particles.

These physical defects, detectable at the dispensing point, lead to quarantine and investigation of the affected batches, followed by regulatory actions. Such defects could result from poor manufacturing practices, inadequate storage, and improper transportation, including through varied climatic conditions.

Enhancing Consumer Participation in Reporting All Drug-Related Defects: Role of HCP

Research indicates that some ADR signals, undetected in clinical trials and unreported by HCPs, were identified through widespread consumer reporting. Rare and severe ADRs are more likely to be identified when consumers, motivated to report, contribute to a significant volume of reports.

We therefore propose including various drug-related complaints (like visible quality defects, and lack of efficacy) in voluntary consumer medical reporting systems, enhancing early detection, and reducing the risk of exposing patients to defective drugs.

Key strategies for improving consumer reporting of drug-related complaints include.

1. Educational campaigns and awareness programs. NDA is utilizing diverse media channels, such as social media, television, and print, in collaboration with healthcare providers, to amplify these messages to reach a wider patient base.

2. Simplifying and making reporting systems more accessible is crucial. NDA is developing user-friendly tools like online forms, mobile apps, and toll-free lines to motivate public participation. Ensuring these platforms are multilingual and accessible to those with disabilities is essential to reach a broad audience.

3. The active role of healthcare professionals and consumers is paramount. Doctors, nurses, and pharmacists are encouraged to gather and report drug-related feedback (like visible quality defects, and lack of efficacy) from patients and relay this information to NDA for investigation.

PHARMACOVIGILANCE AWARENESS CAMPAIGNS ON MAINTSREAM MEDIA

The NPC conducts regular pharmacovigilance awareness campaigns to the general public and health care professionals with the aim of raising awareness about drug safety amongst these stakeholders. The purpose of this is to encourage them to be vigilant, especially while using medicines and report all drug related problems to NDA.

With funding from the Global Fund, through ministry of health, the NPC was able to run awareness campaigns about medicines safety on various mainstream media platforms including radio and television stations. Radio and Television stations with top most listenership and viewership respectively (as per the IPSOs reports) were selected to air SPOT pharmacovigilance adverts produced in the different local languages for a period of 3 months. Live radio and TV talk shows were also held once every month in each of the stations to further emphasize the aspect of medicine safety and reporting drug reactions to the NPC.

Figure 16: Dr. Odipiyo Francis (Inspector of Drugs and Twaha Ibrahim during a radio talk show at Pacis FM in Moyo

Figure 17: Dr. Mwesigwa Douglas (Regulatory Officer) conducting a radio talk show at Karamoja FM

In total, 65 radio talk shows were held in various radio stations across the country (as listed below). Additionally, 4 Pharmacovigilance SPOT adverts were aired in these radio stations per day for a period of 3 months.

Region	Radio stations
Central	• Capital FM • CBS FM
South Eastern	• NBS Khodeyo FM - Jinja
Eastern	• East FM – Tororo • Radio 9, Toracis FM – Bukwo • Karamoja FM – Kotido • Open Gate FM – Mbale • Kyoga Veritas FM – Soroti • Etop FM - Soroti
West Nile	• Arua One FM • Paidha FM – Zombo • Pacis FM - Moyo
Northern	• Rupiny FM – Gulu • Voice of Lango - Lira
Western	• Liberty FM – Hoima • Kibanda FM – Kiryandongo • Kasese Guide FM • Voice of Tooro – Fort Portal • Kagadi Broadcasting Services
South Western	• Radio Sheema • Vision Radio – Mbarara • Kanungu FM • Kazo FM • Radio Rukungiri • Voice of Kigezi – Kabale • Voice of Muhabura - Kisoro

Additionally, 5 TV talk shows were held in 5 TV stations with a nationwide coverage. 4 Pharmacovigilance SPOT adverts were played in these TV stations per day for a period of 1 month. The TV stations where the SPOT adverts were run and talk shows held were; NTV, Bukedde 1 TV, UBC, TV West and WanLuo TV.

Figure 20: Dr. Odipiyo Francis (Inspector of Drugs) during a live TV talk show on UBC

LOCAL SAFETY LABEL VARIATIONS OCTOBER TO DECEMBER 2023

Product Name	Licence Holder	Summary of Approved Changes	Date of NDA Approval
Sodium valproate.	Sanofi Aventis Kenya Limited	Update of Summary of Product Characteristics Eur. (Epilim Chrono®) (SmPC) and Patient Information Leaflet (PIL) to include potential for reproductive toxicity following exposure to valproate in childhood.	**6th December 2023**
Diclofenac sodium (Diclo-denk®)	Denk Pharma Gmbh & Co Kg	Update of SmPC and PIL to add information on what to know before you use Diclo-denk rectal, warnings and precautions, other medicines and possible side effects sections.	**7th November 2023**
Azithromycin monohydrate (Azithro-denk®)	Denk Pharma Gmnh & Co Kg	Update to product SmPC and PIL to add QT prolongation in the warning and precautions section 2 for the PIL and 4.4 for the SmPC.	**7th November 2023**
Desloratadine (Aerius®)	MSD (Pty) Ltd	Change in the summary of product characteristics and patient information eaflet of Aerius to include depressed mood and eye dryness with a frequency of "unknown" in sections 4.8 (undesirable effect) of the SmPC and section 4 (Possible side effects) of the PIL.	**19th October 2023**

Rivaroxaban (Xarelto®)	Bayer Healthcare Ag	To add a new ADR ('eosinophilic pneumonia) with the frequency 'very rare' to the SmPC/PIL due to new pharmacovigilance data.	**7th November 2023**
Carbamazepine (Tegretol®)	Novartis Pharma Services Inc	Update to SmPC and PIL as follows: **Section 6: Warnings and precautions:** Addition of angioedema and anaphylaxis under hypersensitivity reactions. **Section 8: Interactions:** Addition of biviracetam under agents that may raise the active metabolite carbamazepine-10, 11-epoxide plasma levels. **Section 9: Pregnancy, lactation, females and males of reproductive potential:** addition of risk of neurodevelopmental disorders among children exposed to carbamazepine during pregnancy.	**2nd November 2023**
Diclofenac sodium (Diclo-denk®)	Denk Pharma GmbH & Co. Kg	Addition of a warning that the product contains lactose to the folding box.	**19th October 2023**
Sodium valproate Ph, Eur (Epilim®)	Sanofi Winthrop Industries	Update of section 5.3 in the SmpC to indicate the potential for impairment of fertility in males from non-clinical data (exposure in adults and juveniles).	**12th October 2023**
Fexinidazole (Fexinidazole Winthrop®)	Sanofi Aventis Kenya Limited	Update of PIL and SmPC to add suicidal ideation to the neuropsychiatric adverse reactions in section 4.8.	**4th October 2023**

Foreign Safety Label Variations October to December 2023

Source: WHO Pharmaceuticals Newsletter No. 4, 2023

Health Canada - Sulfamethoxazole, trimethoprim

Risk of haemophagocytic lymphohistiocytosis (HLH)

Health Canada has announced that the product safety information for combination sulfamethoxazole and trimethoprim-containing products will be updated to include the risk of haemophagocytic lymphohistiocytosis (HLH). HLH is a condition where large numbers of white blood cells build up in, and damage organs and destroy other blood cells.

Combination sulfamethoxazole and trimethoprim is a prescription antibiotic medicine indicated for the treatment of various bacterial infections, such as urinary tract infections, respiratory tract infections, and gastrointestinal infections.

Triggered by a labelling update for these products by the EMA, Health Canada reviewed the available information from the Canadian and international databases.

Of the ten cases assessed, one case was found to be probably linked to the use of the medicine, eight were found to be possibly linked (including one fatal case) and one (another fatal case) was unlikely to be linked.

The review found a possible link between the use of the medicine and the risk of HLH.

Reference: Health Product InfoWatch, Health Canada, (link to the source within www.hc-sc.gc.ca)

Health Products Regulatory Authority - Tramadol

Risks of sleep-related breathing disorders, adrenal insufficiency and serotonin syndrome

The Health Products Regulatory Authority (HPRA) has announced that the product information for tramadol has been updated to include the risks of sleep-related breathing disorders and adrenal insufficiency, as well as an update to the information on serotonin syndrome.

Tramadol is a centrally acting synthetic opioid analgesic indicated for the treatment of moderate to severe pain.

Following a review of available data, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updates to warnings and precautions as follows:

- Tramadol can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. The risk of CSA increases in a dose-dependent fashion.
- Tramadol may occasionally cause reversible adrenal insufficiency, requiring monitoring and glucocorticoid replacement therapy.
- Serotonin syndrome has been reported in patients receiving tramadol alone or in combination with other serotonergic agents.

Reference: Drug Safety Newsletter, HPRA, (link to the source within www.hpra.ie)

Medicines Control Authority of Zimbabwe (MCAZ) - Azithromycin

Risk of fatal heart rhythms

The Medicines Control Authority of Zimbabwe (MCAZ) has alerted health-care professionals on the risk of fatal heart rhythms with azithromycin.

Azithromycin is a macrolide antibiotic and is indicated for the treatment of various infectious diseases. The product information contains information on the risks of QT interval prolongation and torsades de pointes as well as the results of a clinical QT study which showed that azithromycin can prolong the QTc interval.

Health-care professionals should consider the risk of fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk of cardiovascular events. Alternative medicines in the macrolide class, or non-macrolides such as fluoroquinolones, also have the potential risks of QT prolongation or other significant adverse events that should be considered.

Reference: Medicine Information Bulletin, MCAZ, (link to the source within www.mcaz.co.zw)

European Medicines Agency (EMA) - Fluoroquinolone antibiotics

Reminder of risk of long-lasting, disabling and potentially irreversible adverse reactions

The PRAC of the EMA is reminding health-care professionals by issuing a Direct Healthcare Professional Communication (DHPC) that the use of fluoroquinolone antibiotics, given by mouth, injection or inhalation, is restricted due to the risk of disabling, long-lasting and potentially irreversible adverse reactions affecting several, sometimes multiple, systems, organ classes and sense.

Fluoroquinolone medicines are a family of broad-spectrum antibiotics including iprofloxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin. They are used to treat certain types of serious infections when other antibiotics are not suitable.

Restrictions on the use of fluoroquinolone antibiotics, introduced in 2019 following an EU-wide review of these

very rare but serious adverse reactions, mean that they should not be used to treat infections that might get better without treatment or by other recommended antibacterial medicines, or to prevent traveller's diarrhoea or recurring lower urinary tract infections. Importantly, fluoroquinolones should be avoided in patients who have previously had serious adverse reactions with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and in those who have had an organ transplantation. Combined use with corticosteroid should be avoided.

A study, which evaluated data from the primary care setting in six European countries between 2016 and 2021, suggests that the measures taken to restrict the use of these medicines as a result of the EU-wide review had a modest impact. Although the use of fluoroquinolone antibiotics has reduced, these medicines may still be prescribed outside of their recommended uses.

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

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of long-lasting and disabling effects in Europe)

United Kingdom - Glucose solutions

Medication error: accidental use instead of saline solutions in arterial lines

The MHRA has reminded health-care professionals of the risk of medication error of accidentally using glucose solutions instead of saline solutions as flush fluid for arterial lines, which may contaminate blood samples and result in falsely high glucose readings. This may lead to inappropriate insulin administration and subsequent hypoglycaemia.

Flush fluids are used to maintain the patency of arterial lines when used for the continuous monitoring of blood pressure. The selection and attachment of the wrong flush fluids to arterial lines is a recognized risk, and incidents of serious clinical harm have occurred as a result. Discarding dead volume fluid is not sufficient to prevent blood contamination following the use of glucose in the flushing system.

Health-care professionals should use saline solutions (0.9% sodium chloride) to flush arterial lines and use pressure infusion bags with transparent windows to ensure that the fluid label is always visible.

Reference: Drug Safety Update, MHRA, (link to the source within www.gov.uk/mhra)

European Medicines Agency (EMA)

- Hydroxyprogesterone

Potential risk of cancer in people exposed in the womb and lack of effectiveness

The PRAC of the EMA is reviewing medicines containing hydroxy-progesterone following concerns about the safety and effectiveness of these medicines.

In the EU, these medicines are available as hydroxy-progesterone caproate and are given as injections to prevent pregnancy loss or premature birth in pregnant women and for treatment of various gynaecological disorders, including disorders caused by the lack of progesterone.

The review has been initiated following a study showing that people who were exposed to hydroxyprogesterone caproate in the womb may have an increased risk of any cancer particularly when the medicine was used during the first trimester of pregnancy and with increasing dosage. Its use in the second or third trimester appeared to further increase the risk of cancer in the offspring for males but not for females. Also results from a second study (PROLONG Study) suggested that hydroxyprogesterone caproate is no more effective than placebo in preventing recurrent premature birth or medical complications due to prematurity in the newborn infant.

EMA will communicate PRAC's recommendations once the review has concluded.

Reference: Patients and carers, EMA, (link1 and link2 to the source within www.ema.europa.eu)

The Medicines and Healthcare products Regulatory Agency - United Kingdom - Oral anticoagulants

1. **Reminder of dose adjustments in patients with renal impairment**

The MHRA has reminded health-care professionals of the current advice to ensure that all patients with renal impairment receive an appropriate dose of direct-acting oral anticoagulants (DOACs) medicines due to the increased risk of bleeding.

DOACs include apixaban, dabigatran, edoxaban, and rivaroxaban.

Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose adjusted for renal function. Renal function in adults should be assessed by calculating creatinine clearance. Patients with renal impairment should be reviewed regularly to ensure ongoing efficacy and safety, with dosing adjusted as required.

For paediatric use of these medicines, health-care professionals should counsel parents and caregivers about the reconstitution and dosing of dabigatran granules and rivaroxaban granules to reduce the risk of medication errors.

Reference: Drug Safety Update, MHRA, (link to the source within www.gov.uk/mhra)

2. **Ongoing assessment of abnormal uterine bleeding**

New Zealand. The Medsafe is reviewing the risk of abnormal uterine bleeding (changes to normal menstrual periods) in individuals using oral anticoagulant medicines.

The Centre for Adverse Reactions Monitoring (CARM) received four reports relating to abnormal uterine bleeding with rivaroxaban during monitoring period. No reports were received for apixaban, dabigatran or warfarin. Currently the data sheets for oral anticoagulants list bleeding and/or urogenital.

To increase awareness about this adverse reaction, the Medsafe will issue an article about oral anticoagulants and abnormal uterine bleeding. The benefit risk balance for oral anticoagulants (apixaban, rivaroxaban, dabigatran, and warfarin) remains positive.

Reference: Safety Communications, Medsafe, (link to the source within www.medsafe.govt.nz)

Therapeutic Goods Administration (TGA)
- Australia - Oral anticoagulants
Potential risk of anticoagulant-related nephropathy (ARN)

The Therapeutic Goods Administration (TGA) has announced that the product information for all oral anticoagulants has been updated to include the potential risk of anticoagulant-related nephropathy (ARN). This is a rare but serious adverse event resulting from profuse glomerular bleeding. It has the potential to cause irreversible kidney damage and death. Although rare, ARN is likely to be underdiagnosed as a cause of acute kidney injury. Oral anticoagulants include factor Xa inhibitors - apixaban (Eliquis®) and rivaroxaban (Xarelto®), direct thrombin inhibitors - dabigatran (Pradaxa®), vitamin K antagonists - warfarin (Coumadin®, Marevan®) in this class of medicines. They are indicated for the prevention and treatment of thromboembolic conditions.

The TGA investigated a safety signal of reports of ARN in patients taking oral anticoagulants and sought expert advice from the Advisory Committee on Medicines (ACM) that reported it was well documented in the medical literature with warfarin and other oral anticoagulants. The ACM supported the class-wide warning due to the wide use of the medicines and seriousness of this adverse event. The ACM did not consider a warning for parenteral anticoagulants currently because they are mainly used in hospitals and for a shorter duration.

Health-care professionals are advised that acute kidney injury may occur in patients with altered glomerular integrity or with a history of kidney disease, possibly in relation to episodes of excessive anticoagulation and haematuria or even without pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).

Reference: Safety updates, TGA, (link to the source within www.tga.gov.au)

Valproate

New study on potential risk of neurodevelopmental disorders (NDDs) in children after paternal exposure

1. European Medicines Agency (EMA): The PRAC of the EMA is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived when fathers were taking valproate at the time of conception.

The review is focussing on data from a retrospective observational study conducted by companies using multiple registry databases in Denmark, Norway and Sweden. Initial results of the study may indicate an increased risk of NDDs in children born to men taking valproate up to three months before conception.

However, the PRAC has identified important limitations with the data from the study. In particular, the PRAC had questions about the definition of NDDs used in the study and the specific type of epilepsy the patients had.

The latter is important because valproate may be prescribed more often for some types of epilepsy which are associated with NDDs.

In addition, the companies informed the PRAC about errors in the Norwegian database; the impact of these errors is not yet known.

The PRAC has therefore requested companies to provide analyses of corrected data and will review the required data as they become available.

Male patients being treated with valproate should not stop taking their medicine without consulting their doctor, as their epilepsy or bipolar disorder could become worse.

Patients who have any questions about their treatment should seek advice from their health-care professional.

Reference: Press release, EMA, (link to the source within www.ema.europa.eu)

2. **The Medicines and Healthcare products Regulatory Agency - United Kingdom:** The MHRA has announced that it has been informed by Sanofi (MAH of Epilim®) of errors that may impact the results of study on outcomes in children whose fathers took valproate at the time of conception.

   As a result, the researchers from the original study are conducting a full re-analysis before any final conclusions can be drawn.

The Commission on Human Medicines (CHM) has advised that further guidance in respect of risks in children of men taking valproate should be based upon data that are accurate and complete.

As soon as the revised study analysis is available, it will be re-assessed by the MHRA.

The MHRA advice that no action is currently needed for patients, and that no one should stop taking valproate without advice from their health-care professional.

Reference: News and communications, MHRA, (link to the source within www.gov.uk/mhra)

3. **The Health Sciences Authority (HSA) - Singapore:** The Health Sciences Authority (HSA) has announced that a Dear Healthcare Professional Letter (DHCPL) has been issued to inform health-care professionals of new safety in formation regarding a higher risk of NDDs in children after paternal exposure to valproate as compared to lamotrigine or levetiracetam.

Health-care professionals are advised to inform male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, it is recommended for health-care professionals to discuss with the patient the need for effective contraception.

Reference: Announcements, HSA, (link to the source within www.hsa.gov.sg)

4. **The New Zealand Medicines and Medical Device Safety Authority (MedSafe):** The Med safe has announced that the product information for valproate has been updated to include the potential risk of NDDs in children whose fathers were treat

Health-care professionals are advised to inform patients of this potential risk and consider alternative treatment options for those wishing to father a child and discuss the need for effective contraception when starting sodium valproate and periodically throughout treatment.

Reference: Safety Communications, Medsafe, (link to the source within www.medsafe.govt.nz)

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