UGANDA
NATIONAL DRUG AUTHORITY
Safe Drugs Save Lives

PHARMACOVIGILANCE Bulletin

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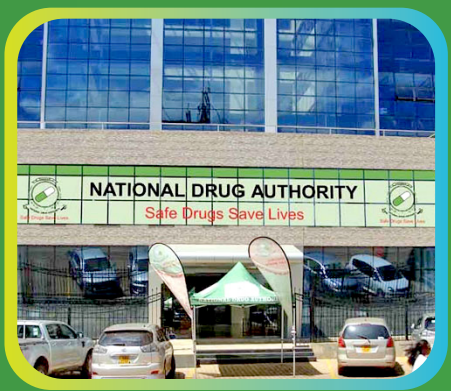
IN THIS ISSUE



Editorial Team:

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Foreword

We welcome you to this issue of the Pharmacovigilance bulletin.

The National Pharmacovigilance Centre has received overwhelming support and collaboration from the health workers and general public in reporting adverse events following vaccination with the Covid vaccine. The USSD code alone yielded over **14,000** responses with the most commonly reported reaction being general body weakness. All the reported reactions are labelled by the manufacturer and expected.

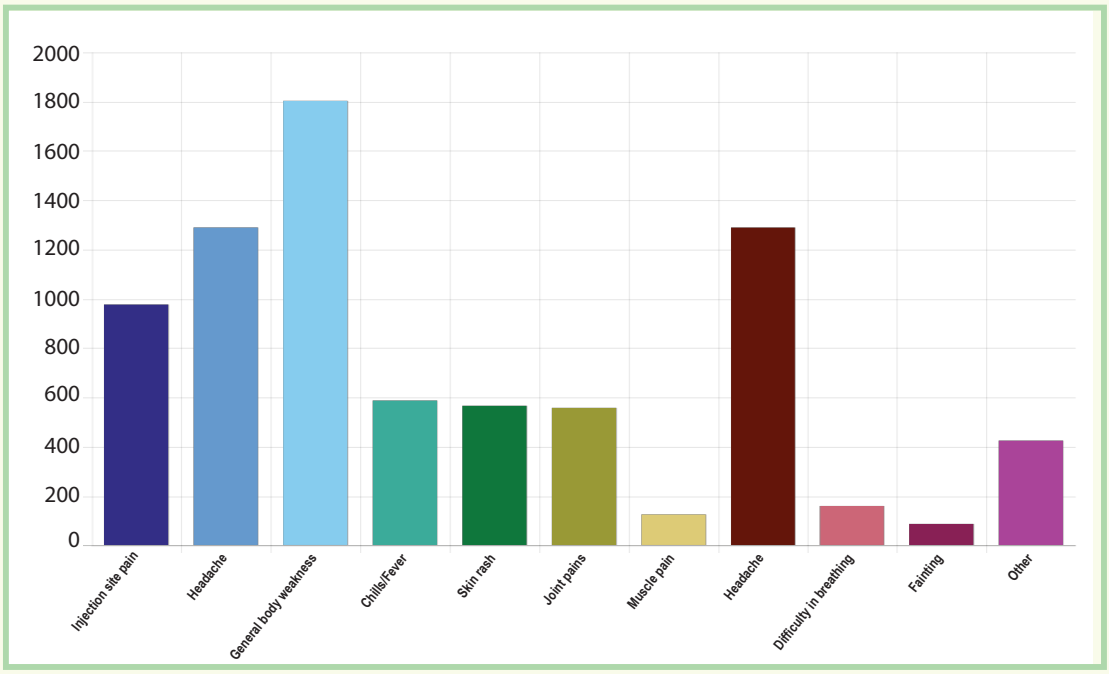
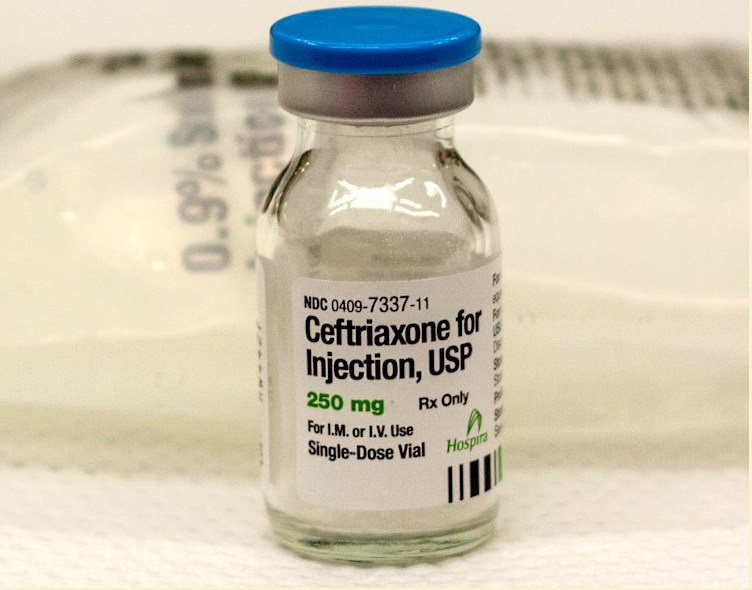


Figure 1. Commonly experienced reactions submitted through the USSD code



With the recent notification of Covidex as a supportive treatment for Covid, this bulletin emphasizes the need for pharmacovigilance for herbal medicines.

However, other drugs (and other diseases!) still need vigilance and therefore we have featured a case report of a fatal anaphylactic reaction following Ceftriaxone administration and the regulatory decisions that have been made over time towards promoting safe use of antibiotics.

The Med Safety mobile application which has a dedicated option for reporting reactions to the Covid vaccine has been in use in Uganda for over a year now. We take a look at its usage statistics and how it can be utilised further.

One of the roles of the pharmacovigilance centre is to identify emerging signals from the case reports received. In this regard, we have included a report on forgetfulness with Dolutegravir which is an unconfirmed signal still under review.

Read on for more of the quarterly updates including safety label variations and ADR analysis.

Stay Safe

COVID-19 Vaccine Safety Monitoring:

By Ismail Ntale

How are vaccine-related adverse events monitored by NDA?

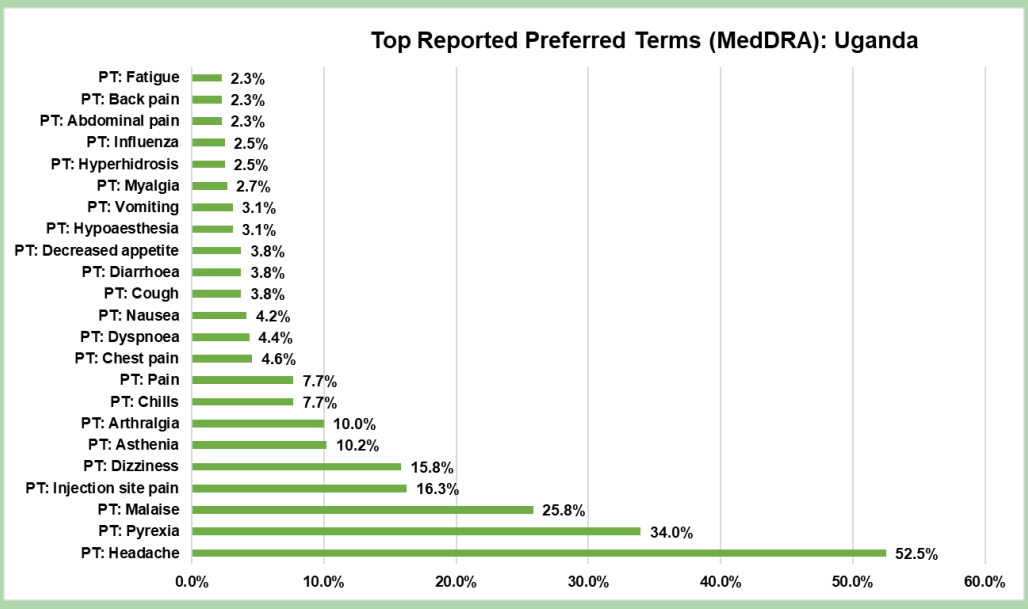
Reporting adverse events is a critical part of monitoring vaccine safety once a vaccine has been rolled out to the broader population. This monitoring relies on the timely reporting of minor and severe Adverse Events Following Immunization (AEFIs), allows of investigations and enables causality assessment. In addition, data on rare adverse events, or adverse events with a slow onset, can only be detected when vaccines are used by a large number of people and when these events are actually being reported.

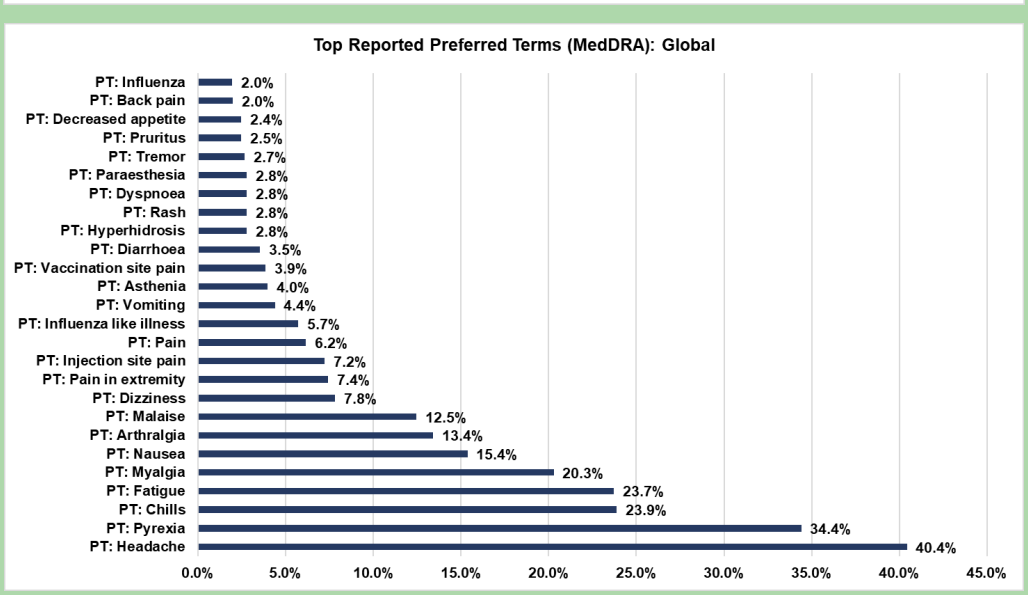
As with all new vaccines, the rollout of COVID-19 Vaccines necessitates effective safety monitoring systems to be put in place not only to detect and investigate adverse events following immunization(AEFIs) but also to respond to rare adverse events not detected in pre-licensure clinical trials. National Drug Authority set out to strengthen the Pharmacovigilance system even in the COVID-19 context.

Several reporting platforms were availed to the public and healthcare workers to enable reporting of AEFIs. These include the NDA toll free line, WhatsApp number and SMS platform using USSD code among others.

Since the roll out of the COVID-19 vaccination, NDA has received a total 0f 651 AEFI reports of reactions to the Astra Zeneca Covid-19 vaccine. Of these cases reported, 11 were reported as serious and all have been investigated in collaboration MOH, UNEPI and WHO.

Common adverse events reported are presented below. Generally, the events reported in Uganda are not any different from those reported elsewhere.





Don't forget to report an AEFI!

Ideally, an AEFI should be reported immediately. This allows an investigation to be carried out by a multi-disciplinary team at the district, regional or national level, being composed of NDA, Ministry of Health (MOH), District Local Government (DLG) and co-opted experts to generate an AEFI investigation report that enables causality assessment conducted by the National AEFI committee to determine whether the event may have been caused by the vaccine or whether it was a coincidental event. This procedure also applies to clusters, rare events or any other events of concern. The outcome of the causality assessment is given to the ministry of health for further communication.

REPORTING PLATFORMS AVAILABLE

Dial ***284*99#** and follow the prompts

Toll free **0800101999**

WhatsApp **0791415555**

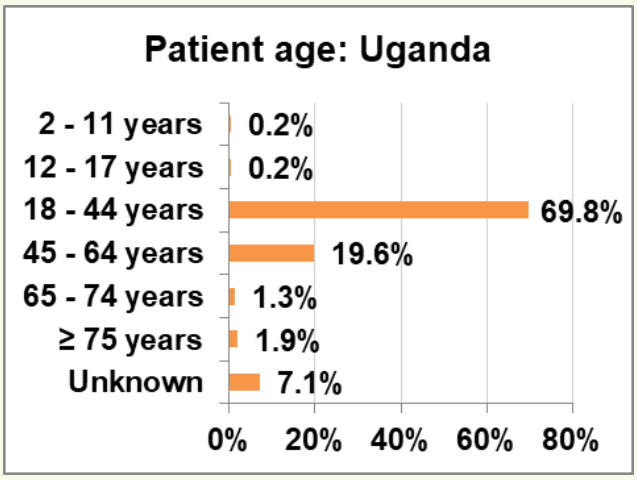
Med Safety App that can be downloaded from Google Play Store or Apple Play store

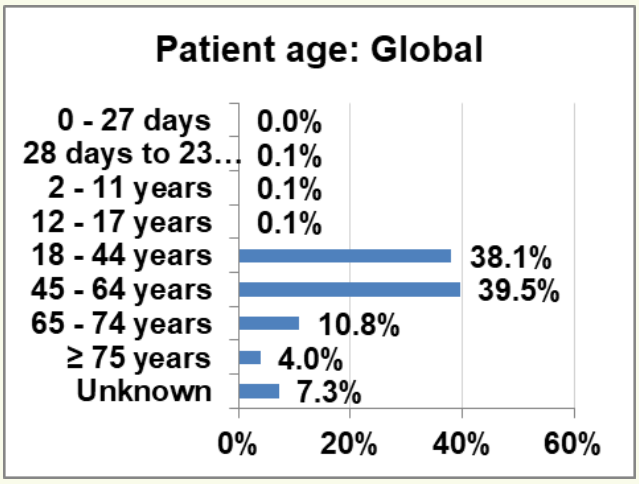
Paper-based available COVID-19 vaccination centers.

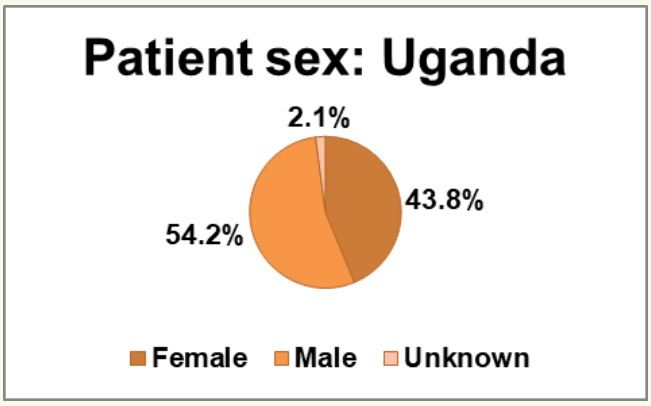
MOH Toll free line **0800200600**

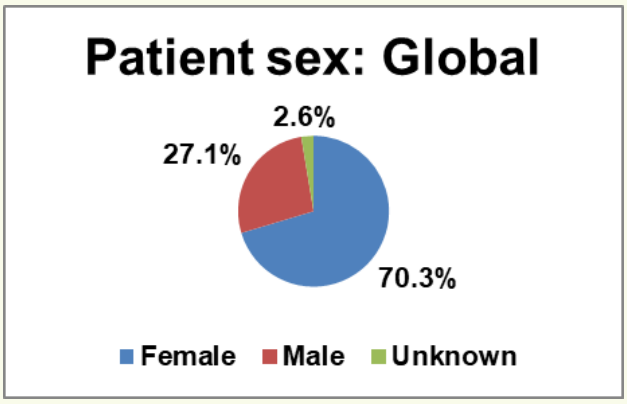
NDA website and report online

A comparison of AEFI reports received in Uganda versus other countries:



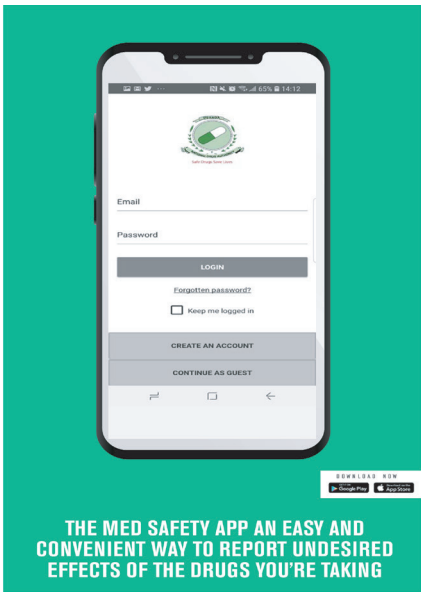




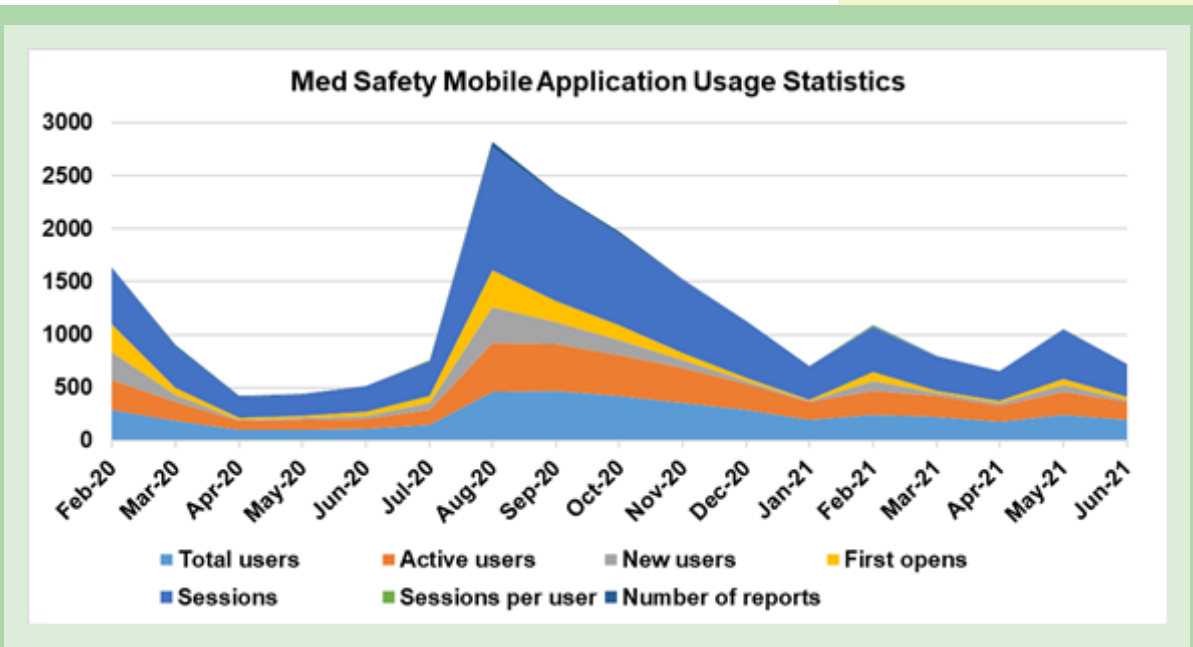


One Year On: Med Safety Performance in Uganda

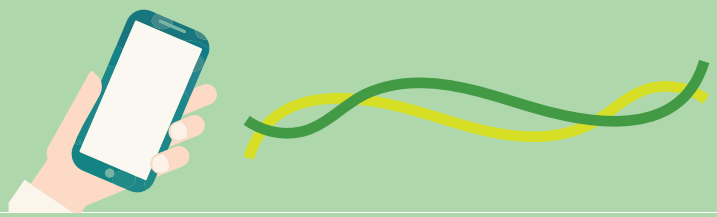
NDA's Med Safety Mobile App



Uganda launched the Med Safety Mobile app on February 26th 2020. Since then, over 180 reports have been submitted through this channel, with approximately 200 total users averaging 2000 sessions. This is a review of the performance of the app during the one year it has been in use.



After the initial peak in downloads and usage due to the launch, the app usage has settled to a steady download and usage rate of 200 daily active users. There is still room for improvement and this is to encourage all smart phone users to download and use the app.



200
daily active users

Why should you download the app?

The Med Safety app is a free smart phone app for reporting suspected adverse effects (or adverse drug reactions) to the National Drug Authority. This simple tool lets you report adverse effects to medicines, keep track of previously reported information and receive official news and alerts about medicines you are taking or interested in.

Why use the app?

- Quick and easy to report adverse effects
- Instant access to medicines safety information
- Help make medicines safer for all
- It's free!

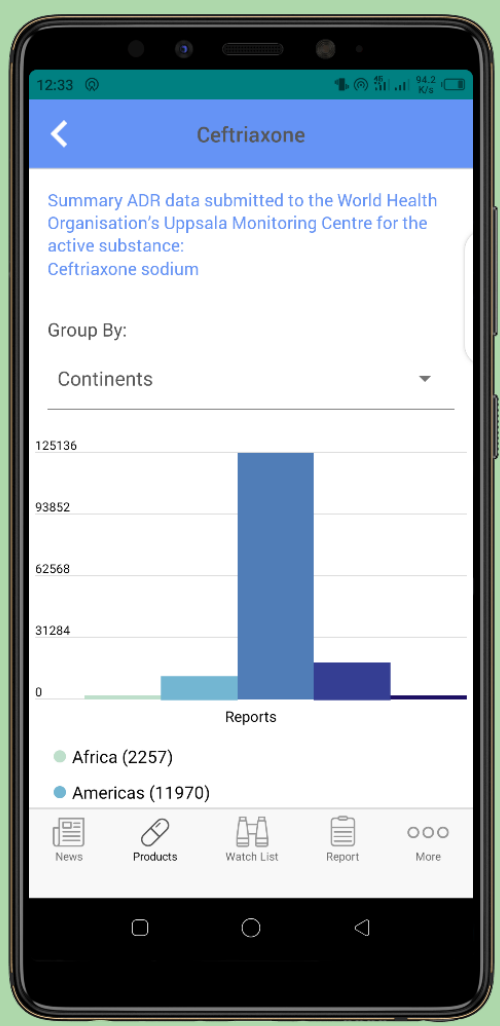
Key features of the app

- Submit reports on adverse effects even while offline
- View and submit updates to previously submitted reports
- See immediate acceptance of your reports
- Create a 'watch list' of medications to receive personalised news and alerts

Why does it matter?

Medicines are developed to be as safe and effective as possible, but they can still cause side effects. It is important for people to report adverse effects to medicines as this information can be used to identify previously unknown issues with those medicines.

Adverse effects sometimes stop patients from completing their treatment, which can lead to even more serious problems. Reporting adverse effects encourages a dialogue between patients and healthcare professionals and helps professionals to identify and investigate unknown or poorly described adverse effects.



Case Report: Medication Error with Intravenous Ceftriaxone

The National Pharmacovigilance Centre received a report of an anaphylactic reaction in a child following administration of Ceftriaxone injection.

Dr. Ian Mugisa

The case report involved a one-and-a-half-year-old male child presenting with a history of fever, vomiting, diarrhoea and cough for one month. Consent to treat the child was obtained from the mother prior to obtaining history. The child also had a history of convulsions for two weeks prior to visiting the clinic. On physical examination, crackles were heard during the chest examination and oedema of the limbs was observed. Investigations performed included a blood smear (BS) which revealed no Malaria parasites as well as a Complete Blood Count (which showed low platelets, low neutrophils, low lymphocytes and low Haemoglobin). A diagnosis of septicaemia with diarrhoea was made and the Child was admitted. Intravenous Ceftriaxone was prescribed for this child at a dosage of 1g per day. After the first two days of admission, the patient experienced some adverse reactions to Ceftriaxone administration (difficulty breathing and collapsing). The treatment was changed to IV Ciprofloxacin 58 mg over the next three days. The patient showed signs of improvement. On the sixth day of admission, there was a routine staff shift change bringing in a nurse who was not aware about the child's allergy to ceftriaxone or the update to the treatment. 1g Ceftriaxone was administered intravenously. The child collapsed and was promptly resuscitated with IV fluids, Adrenaline and Cardio-Pulmonary Resuscitation (CPR).

The CPR (bagging, Chest compressions, and high flow oxygen by CPAP) were able to restore the pulse (PR 105 beats per minute) and spontaneous breathing (Respiratory rate 20-25). However, the child's pupils remained undilated and non-responsive to light, so the clinicians continued with bagging for close to 3 hours. Other treatments given during resuscitation included chlorpheniramine and nebulization with salbutamol. Despite all the concerted efforts and aggressive resuscitation, the child continued to deteriorate and eventually succumbed to the reaction and died.

Discussion:

The 2016 Uganda Clinical Guidelines (UCG) page 388 recommends the administration of 1g Ceftriaxone IV daily for sepsis and toxaemia until the patient is able to take Ciprofloxacin orally to complete 7 days. It is noted that the treatment administered to the child was mostly in line with the UCG.

However, a medication error occurred when the new shift nurse was unable to notice the update in the patient's notes pertaining to the record of allergic reaction to Ceftriaxone in the patient file. This was inadvertent considering that this nurse had been away and wasn't knowledgeable about the allergic reaction.

Much as it is common practice to write an indication of allergy at the top of the Patient's file and this practice often works, it still has some challenges considering that a single nurse is often responsible for administering IV medications to many patients on a ward.

Recommendations :

1. Additional ways such as colour coded Allergy wrist bands could be utilised as a safeguard.
2. Health Care workers are advised to report any Adverse Drug Reaction (ADRs) to the National Pharmacovigilance Center using the Toll Free line 0800 101 999, the Whatsapp line 0791415555 or email to **druginfo@nda.or.ug**

Ceftriaxone: Additional Studies and Regulatory Decisions

Diana Kesi Nakitto, Nasser Lubowa, Elijah Kirabira

A recent study by Paul K, et. al 2021, revealed that there was 32.1% inappropriate use of ceftriaxone among health workers in health facilities. Some of the reasons for inappropriate use of ceftriaxone were wrong indication, wrong dose and duration of treatment, lack of lab tests prior to prescribing of ceftriaxone, irrational prescribing and possible drug interactions. Full details of this study can be found using the link below

32.1%
inappropriate use of ceftriaxone

https://www.mdpi.com/2079-6382/10/7/779/pdf

Following this study and reports of Ceftriaxone anaphylactic reactions, a meeting between NDA and MoH made the following policy recommendations on use of ceftriaxone in all Health facilities:

The Antimicrobial resistance strategy (AMR) NAP 2018-2023 should be widely disseminated and implemented in all public and private health facilities in Uganda.

The MoH encourages health workers to make use of the Uganda National formulary alongside the STGs in management of infections

Laboratories at all health facilities should be revamped with the necessary reagents for culture and sensitivity tests and other tests that guide prescribers in determining the right antibiotics to use.

There should be re-establishment and supervision of medicine therapeutic committees in all health facilities to monitor antibiotic use and adherence to the standard treatment guidelines.

Continuing in service medical education and supervision of health workers at the health facilities by the Hospital Directors.

NDA's Post Marketing Surveillance Unit is continuing with targeted surveillance activities to investigate complaints of anaphylactic reactions in other hospitals where the drug is used.

Reference:

Paul Kutyabami, Edson Ireeta Munanura,*Rajab Kalidi, Sulah Balikuna, Margaret Ndagire, Bruhan Kaggwa, Winnie Nambatya, Pakoyo Fadhiru Kamba, Allan Musiimenta, Diana Nakitto Kesi, Victoria Nambasa, Allan Serwanga and Helen Byomire Ndagije. Evaluation of the Clinical Use of Ceftriaxone among In-Patients in Selected Health Facilities in Uganda. Antibiotics 2021, 10, 779. **https://doi.org/10.3390/antibiotics1007077**

Local Safety: Memory loss in patients taking Dolutegravir

Two cases of forgetfulness experienced by clients taking Dolutegravir based regimen have been reported to National Drug Authority.

Case Narratives:

Case 1: NS is a 35-year-old female who was taking TLE before she was transitioned to TLD on 9/2/2021. After several weeks on the new regimen, she started becoming forgetful and this continued until she reported to the clinic. The patient asserts that while on EFV containing regimen, she was well. In view of this, the clinician attending to her decided to put her back on her previous regimen. Seven weeks after withdrawing the drug, the client returned to the clinic for review and reporting that she has recovered and was doing well.

Case 2: AJ is 39 years old female client who was on TLE previously and then transitioned to TLD on 18th/12/2020. One and half months later after transition, the client came back to clinic complaining of forgetting so much. She narrated that when she does something after a short while she does not remember and has to ask herself whether she has done it or where she has placed something. The clinician attending to her suspected Dolutegravir and withdrew it. There was no information on the patient condition after withdraw of the drug at the time of reporting.

Discussion

Memory loss or forgetfulness is not explicitly listed as an event on the product information leaflet of Dolutegravir. However,

neuropsychiatric side-effects including insomnia, sleep disturbance, dizziness, restlessness, anxiety, depression, poor concentration, headache, slowed thinking or pins and needles sensations with no obvious explanation were the most commonly observed neuropsychiatric side-effects of dolutegravir in clinical trials.

There are 7 cases of memory loss reported in the WHO global database and suspected to be related to Dolutegravir but little is available on the description of these cases.

Some degree of memory problems and modest decline in other thinking skills has been attributed to or is part of aging. However, the aetiology of memory loss is multifactorial and ranges from certain drugs to disease and metabolic abnormalities. Vitamin B-12 deficiency, sleep deprivation, use of alcohol, drugs, anesthesia from recent surgery, chemotherapy, head injury lack of oxygen to the brain, certain types of seizures, brain tumor or infection, mental disorders such as depression, thyroid dysfunction, and other illness are possible causes of memory loss.

Tests like (cognitive testing to check thinking ability, blood tests to look for various conditions including vitamin B-12 deficiency and thyroid disease, imaging tests such as magnetic resonance imaging (MRI) or computed tomography (CT) scan, electroencephalogram (EEG) to measure the electrical activity of the brain spinal tap to check for infection, cerebral angiography which is an X-ray to see how blood flows through the brain) help in arriving a final diagnosis.

The two cases involve young adults and age related memory loss is ruled out. One case had a positive dechallenge as the patient's event resolved upon withdraw of DTG. We had no information on dechallenge for the second case. Given however, that neuropsychiatric effects are documented in literature for Dolutegravir, it is possible that these patients could have experienced the drug effect. The National Drug Authority will continue monitoring this adverse event and will be giving regular updates.

Recommendation

Many medical conditions that cause memory loss are treatable when identified early. Referring patient for review by a specialist, such as a neurologist, geriatrician, or mental health professional should be considered before DTG can be considered as suspect.

Withdraw dolutegravir if other possible causes are ruled out and if your patient's quality of life is affected (affects ability to work, live independently or maintain a social life)

Monitor for occurrence of this adverse in patients taking TLD and report to NDA in order to investigate the event further.

Acknowledgement

We acknowledge and appreciate **Ms Justine Kizito** of Nsambya Home Care and **Dr. Adrian Tusiime** of Mbarara Municipal Council Health Centre IV for sharing the case reports and contributing to this article.

The two cases involve young adults and age related memory loss is ruled out. One case had a positive dechallenge as the patient's event resolved upon withdraw of DTG.

Pharmacovigilance for herbal medicine: An illustration with Covidex

A representative mobile phone survey of citizens' views conducted by Twaweza's Sauti za Wananchi in Kampala in Jul-Aug 2020 and Dec-Jan 2021 revealed that the number of Kampala residents who say that if they or a household member contracted Covid-19, they would self-medicate using herbal remedies and/ or steam inhalation has increased over the course of the pandemic. However, the number remains low compared to those seeking expert medical assistance or following official advice to isolate. In December 2020 and January 2021, around one out of five residents would self-treat using herbal remedies (13%) or steam inhalation (6%). Both figures have increased since earlier in the pandemic.

The same survey found that over 30% of the respondents believed that alternative remedies cure covid. However, this is not backed by science and as such, these remedies are used only **supportively** and not curatively for Covid.

National Drug Authority notified Covidex as a **supportive** treatment in management of viral infections.

30%

of the respondents believed that alternative remedies cure covid

Safe Drugs Save Lives

PRESS RELEASE
FOR IMMEDIATE RELEASE

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arwamwiri@nda.or.ug
0784-567474

NATIONAL DRUG AUTHORITY HAS NOTIFIED COVIDEX AS A LOCAL HERBAL MEDICINE.

Kampala, – June 29, 2021. National Drug Authority (NDA) informs the public that after a record time of 14 days of engagements with the innovators and assessments of the product information, Covidex, has been notified to be sold in licenced drug outlets for supportive treatment in management of viral infections **BUT NOT** as a cure of COVID-19. The product should be used under the guidance of a professional health worker. Notification is an initial approval granted to herbal medicines based on evaluation of scientific data to confirm the quality, safety and efficacy of the drug and inspection of the factory for good manufacturing practices.

As you are all aware, on June 14th 2021, NDA released a statement notifying the public that it had not authorized the production, sell and use of Covidex (manufactured by Jena Herbals Uganda Ltd) that had claims of preventing and treating COVID-19. NDA engaged with innovators and an application for notification was submitted on June 15th, initial assessments were scientifically done and a response with further guidance was sent to the innovators within three days! NDA received the answers on June 27th and a comprehensive assessment was undertaken including an inspection of the factory to assess compliance with good manufacturing practices to ensure that the product is of good quality, safe and efficacious. After engagements, the innovators have removed unsubstantiated claims that the product treats and prevents COVID-19 and revised it to ***supportive treatment in management of viral infections.***

NDA has granted Covidex an approval based on initial assessment, published literature and safety studies conducted by the innovator. The product has been formulated from herbal plants that have been traditionally used to alleviate symptoms of several diseases. To further support the efficacy of the drug for other uses, NDA has advised the manufacturer to conduct random controlled clinical trials which are the highest level of evidence to ascertain any claims of treatment.

Safe Drugs Save Lives

As our standard procedure, NDA will continue to monitor the safety of Covidex through our post-market surveillance activities. We call upon the public to immediately report any side effects from use of this product on our toll free line **0800 101 999.**

NDA remains committed to ensuring that all drugs imported, produced and sold in Uganda are of good quality, safe and efficacious as a way of safeguarding public health as empowered by the National Drug Policy and Authority Act cap 206. NDA also prioritises research and development of traditional medicine, that's why we have in place a comprehensive Herbal Medicine Guidelines for local drug research, a herbal unit that engages, trains and provides technical support to herbal medicine manufacturers to improve the quality of their products and with these efforts, in the last 3 years, NDA has authorized over 190 local herbal products and provided technical support through over 70 inspection of local herbal medicine manufacturers.

NDA advises all innovators and manufacturers whose products have not been notified to engage with our team for assistance to have their products assessed. We advise the general public to only buy drugs from licenced drug outlets and avoid self-medication especially of prescription drugs. We encourage everyone to follow Ministry of Health (MOH) guidelines and SOPs and always seek treatment from licenced heath facilities.

ENDS

The manufacturer's patient information leaflet for Covidex cautions that diabetic and pregnant patients should only use the product under the advice of a medical doctor or clinical pharmacist.

This is because herbal medicines, like any other medicines, have side effects and can also interact with other therapies in the patient's regimen.

This is to therefore call upon all users of herbal medicine to remember to remain vigilant even while using herbal medicines and report any side effects promptly to the National Drug Authority on the toll free line **0800101999 or whatsapp 0791415555** or email: druginfo@nda.or.ug

Safety Label Updates

What is a Safety Variation?

The Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) are the basis of information for health care professionals and patients respectively on how to use a medicine safely and effectively. They are updated regularly through the life cycle of a product as new safety or efficacy information emerges.

In Uganda, the majority of our post market information comes from the ADR reports submitted by clinical teams at health centres across the country. Using the information from your submitted reports, NDA is able to write to manufacturers leading to revision of the SmPCs and PILs.

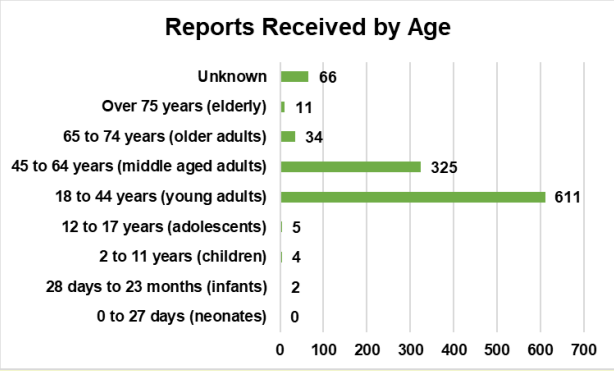
Depending on the new safety information emerging from vigilance, updates can be made to the dosage, contraindications, special warnings, precautions for use, undesirable effects and even packaging in order to keep the medicine safe.

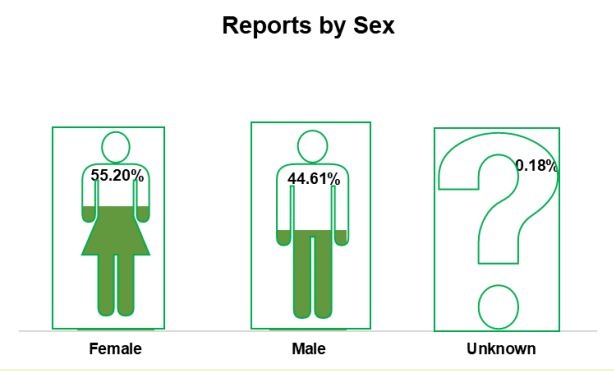
In the period April to June 2021, the following are the updates received from various manufacturers:

Product	Manufacturer	Details
Over The Counter (OTC) NSAIDS (Ibuprofen, ASPIRIN, DICLOFENAC ETC)	FDA Safety Communication to all manufacturers of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	OTC NSAIDS should not be used by pregnant women after 20 weeks as this can cause serious kidney problems in the unborn baby, which can lead to low levels of amniotic fluid and the potential for pregnancy-related complications.
Stocrin (Efavirenz 600 mg)	MSD (PTY) LTD	Update of PIL to include warnings on late onset neurotoxicity including ataxia and encephalopathy
Zinnat (Cefuroxime axetil 250 mg)	GSK	Indications: Bronchitis replaced by obstructive pulmonary disease Dosage: Children above 40kg to be given adult dose
Tramadol Hydrochloride 50 mg effervescent tablets	Denk Pharma	Updated label to include warnings on concomitant use of opioids and Benzodiazepines.
Forxiga (Dapagliflozin 10 mg)	Astra Zeneca	Update of SmPC to include new indication: chronic heart failure with reduced ejection fraction
Septrin (Cotrimoxazole 480 mg)	Beta Healthcare Uganda	Update of SmPC to include new adverse reaction: drug reaction with eosinophilia and systemic symptoms (DRESS)
Tivicay (Dolutegravir 50 mg)	Hetero Labs	Prescribing information update following clinical studies to include warning on potential risk of neural tube defects with Dolutegravir among women of child bearing age and counselling for this group about use of effective contraception while on the drug

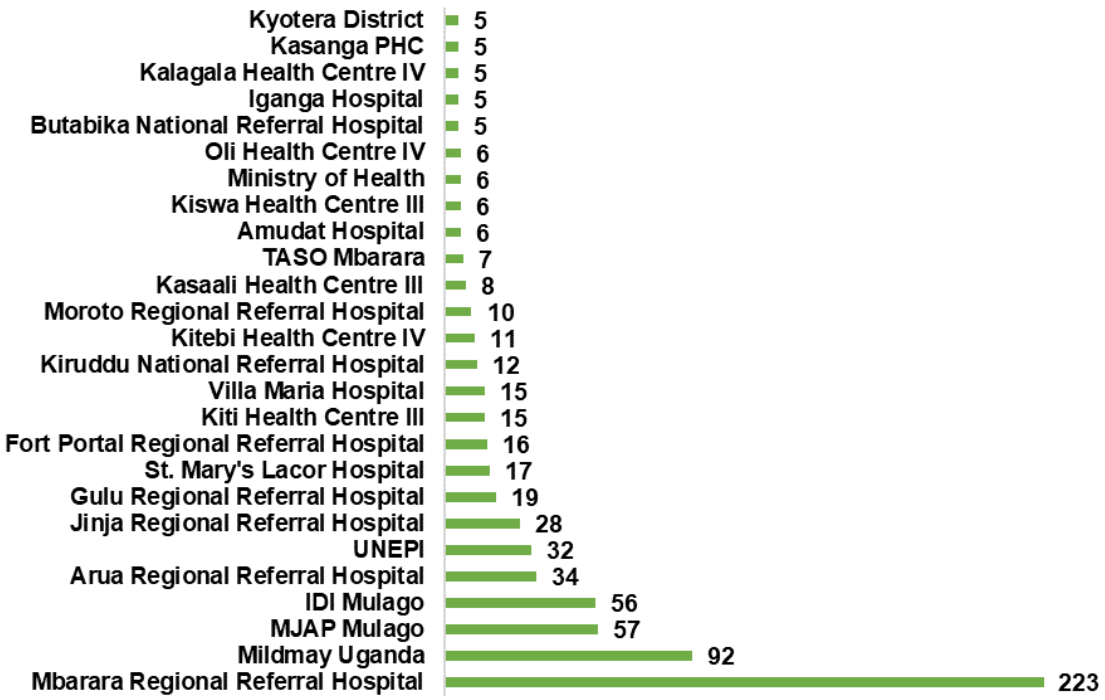
Quarterly ADR Analysis

A total of 1058 reports were submitted in the period 1st April 2021 to 30th June 2021. Of these, 202 were directly sent through the Immunization Programme from the Covid Vaccination exercise. The most commonly reported reactions were headache and injection site pain, which resolved in majority of the vaccine recipients. The reports are characterised below:

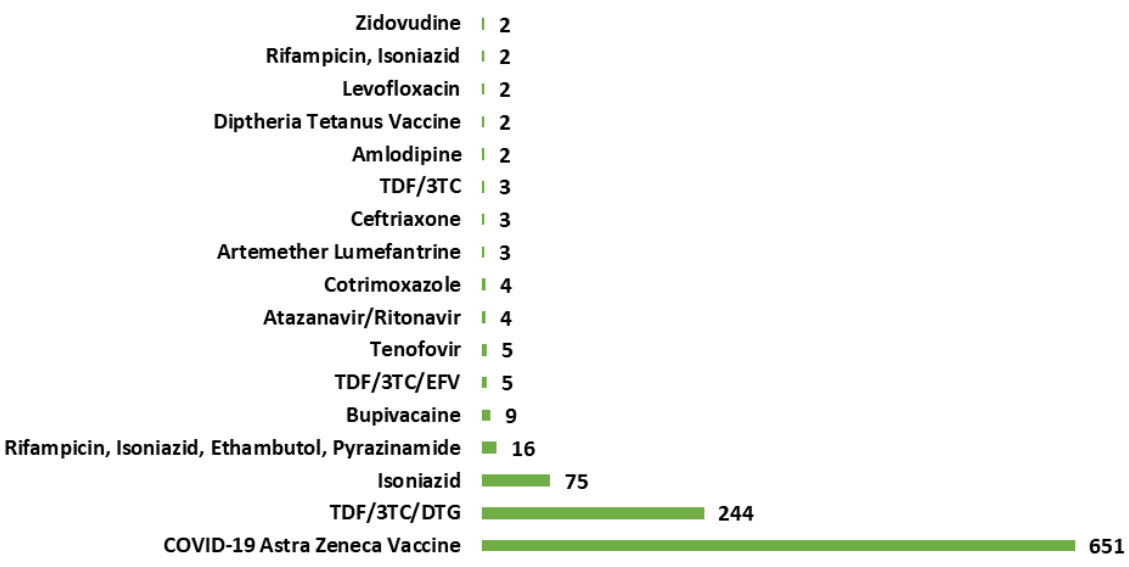




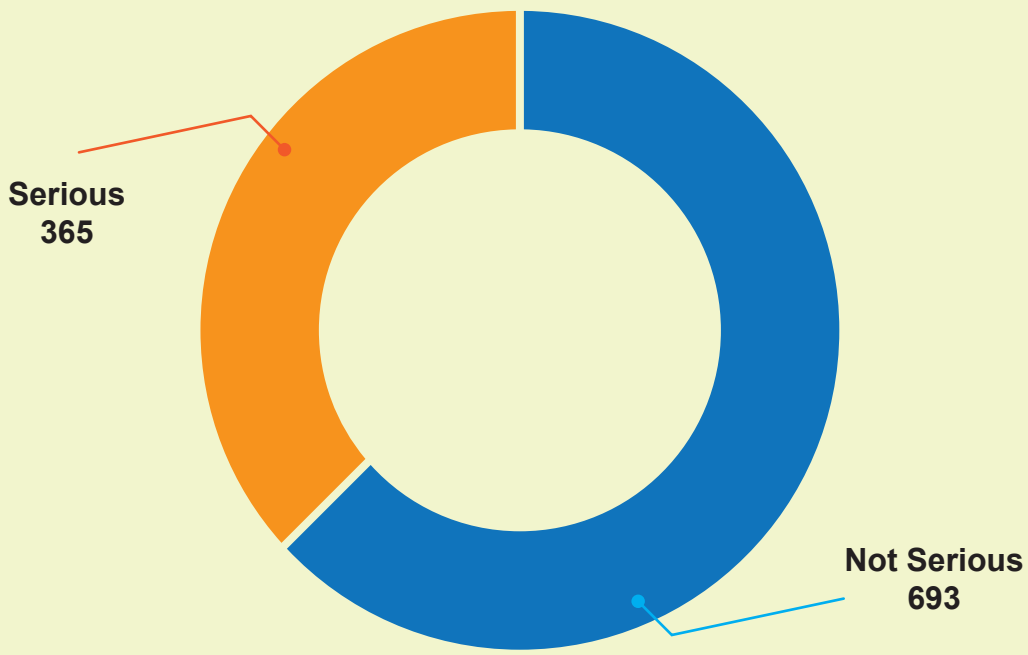
Top Reporters



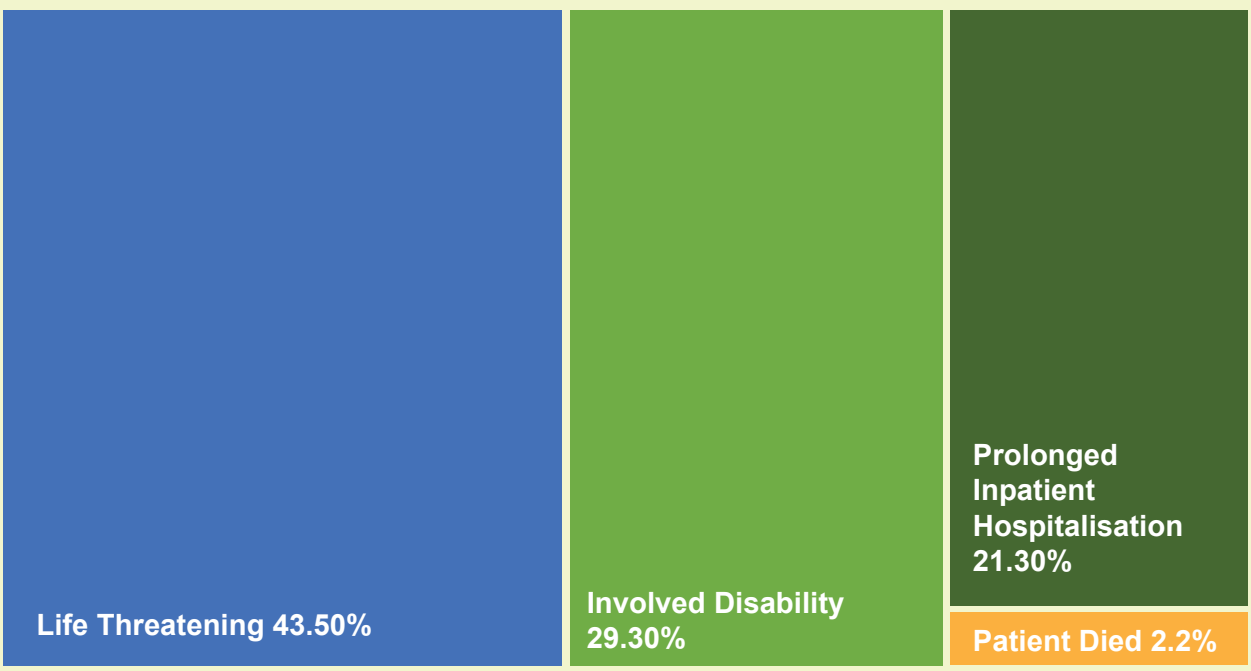
Top Reported Products



Seriousness of Reactions



Reasons for Seriousness



Selected Important Drug Reaction Pairs

Product	Reports	Reactions	Reports
Covid-19 Astra Zeneca Vaccine	**651**	**Headache**	**112**
		Injection site pain	83
		Fever	76
		General body weakness	75
		Dizziness	41
Tenofovir, Lamivudine, Dolutegravir	**244**	**Hyperglycaemia**	**105**
		Erectile dysfunction	11
		Insomnia	6
		Palpitations	5
Isoniazid	**75**	Skin hypersensitivity reaction	20
		Paraesthesia	10
		Hepatotoxicity	9
Bupivacaine	**9**	Severe headache, vomiting, restlessness, confusion	8
		Cardiac arrest	1
Artemether Lumefantrine	**3**	Absence of foetal movements, macerated stillbirth	3
Ceftriaxone	**3**	Skin hypersensitivity reaction	2
		Jaundice, vomiting	1
Amlodipine	**2**	Bilateral lower limb swelling	1
		Loss of consciousness	1
Levofloxacin	2	Prolonged QTC	1
Uva tea	1	Polyuria, weakness, anorexia	1

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NDA Quality Control Laboratory is prequalified by WHO, Geneva; and accredited by ANAB, USA, to ISO/IEC 17025 standard.