The basic concepts in pharmacovigilance

1. The reasons of pharmacovigilance

1. E-learning objectives

At the beginning of this module participants will find a list of historical drug safety issues that led to the withdrawal of a drug from the market.

In addition, the module provides a general overview of the drug development process from the perspective of pharmacovigilance (2.1) itself.

The general objectives of this module are:

- to illustrate how different **drug safety issues** led to the withdrawal of several widely used drugs in the past;
- to inform about the **limitations** of the pre-marketing phase of drug development with regard to drug safety.

2. Medicines withdrawn from the market for safety reasons

In the past years many topics raised awareness and necessity of pharmacovigilance (2.1) (see Table n. 1). Surely, the most famous one was the thalidomide disaster.

Table n. 1 - Examples of medicines withdrawn from the market for safety reasons

Active principle	Years on the market or Year of withdrawal	Reason for withdrawal	Where?
Thalidomide (sedative hypnotic drug)	**5 years (1957 to 1961)**	**Teratogenicity**	**Worldwide**
Chlormezanone (anxiolytic and a muscle relaxant)	1996	Hepatotoxicity & Steven-Johnson Syndrome	European Union, US, South Africa, Japan
Rofecoxib (NSAID)	5 years (1999 to 2004)	Cardiovascular toxicity	Worldwide
My Pikin Baby Teething Mixture (a syrup for teething pain)	Withdrawn in 2008	The product was contaminated with diethylene glicol	Banned in Nigeria

After the "**thalidomide tragedy**" many countries have established drug monitoring systems for early detection and prevention of possible drug-related morbidity and mortality.

3. What's a drug development?

Before a drug gets on the market it must undergo:

- **pre-clinical testing**: *in vitro* and *in vivo* studies on animals evaluating the pharmacokinetics, pharmacodynamics and toxicology of new substances;

- **clinical studies**: phase I, phase II and phase III studies performed on humans to assess the efficacy of a new drug for the indications for which it was studied and to provide a preliminary assessment of its safety and tolerability.

The **information** collected during **the pre-marketing phase** of drug development is inevitably incomplete and **limited** with regard to possible ADRs. This is mainly because:

- the predictive value in humans of pre-clinical trials is limited by the variability of response between different animal species;

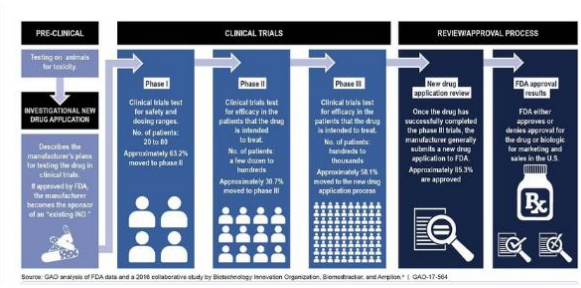
- patients used in clinical trials are selected and limited in number (rarely 10000 patients), making difficult to detect rare adverse reactions;

- the real world population exposed to the drug is very different from the population studied, since subgroups of the such population such as children, the elderly and pregnant women are excluded from clinical trials;

- the limited duration of trials does not enable the identification of delayed reactions;

- information about chronic toxicity or on drug interactions is often incomplete or not available.

So, once a drug gets approved, **pharmacovigilance** comes into play. In fact, post-marketing surveillance is important to enable detection of less common, but sometimes very serious ADRs.



Practical Approach:

The example of thalidomide demonstrates how very astute, alert and observant medical doctors helped to prevent the development of drug morbidity and drug mortality by reporting suspected ADRs.

Therefore, health professionals should report ADRs. You too can make the difference!

1.0 4. Key points

- ✓ in the past many drugs have been withdrawn from the market for safety reasons

- ✓ The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. So, once a drug gets approved pharmacovigilance is necessary and very important.

5. **What's the darkest episode in pharmacovigilance history?**

a. the thalidomide disaster

b. the ibuprofen disaster

c. the amoxicillin disaster

d. the isoniazid history

Teaching:

In the past years many topics raised awareness and necessity of pharmacovigilance. Surely, the most famous one was the thalidomide disaster

ADRs identification occurring throughout the pre-marketing phase is limited by:

a. the large number of patients usually involved in clinical studies

b. the poor degree of variability in terms of response between the subpopulations commonly involved in clinical trials, including children, the elderly and pregnant women

c. **the short time of exposition which does not allow information about chronic toxicity and drug interactions**

d. the prolonged duration of clinical trials

<u>Teaching:</u>

The information collected during the pre-marketing phase of drug development is inevitably incomplete and limited with regard to possible ADRs. This is mainly because:

- the predictive value in humans of pre-clinical trials is limited by the variability of response between different animal species;

- patients used in clinical trials are selected and limited in number (rarely 10000 patients) making difficult to detect rare adverse reactions;

- the real world population exposed to the drug is very different from the population studied, since subgroups of the such population such as children, the elderly and pregnant women are excluded from clinical trials;

- the limited duration of trials does not enable the identification of delayed reactions;
- information about chronic toxicity or on drug interactions is often incomplete or not available

2. Basic definitions in pharmacovigilance

Let's start from the beginning! Let's start with the glossary!

1. E-learning objectives

Some of the **definitions** commonly used in pharmacovigilance (2.1) are listed below, including the definitions of pharmacovigilance (2.1) itself, adverse drug event and signal (2.6).

After reading this module, participants should be able to explain what pharmacovigilance (2.1) is and to define all of its most relevant terms.

2. What is pharmacovigilance?

WHO defines **pharmacovigilance** (PV) as the "science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem" (WHO 2002).

It focuses on investigating and monitoring **adverse drug reactions (ADRs)** after medicinal products are licensed (WHO 1972). The aims of PV consist in enhancing patient care and patient safety in relation to the use of medicines and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.

More: https://www.youtube.com/watch?v=RxbrFG56q9I

3. Definition of adverse event

An **adverse event (AE)** is any untoward medical occurrence that may present during treatment with a pharmaceutical product which does not necessarily have a causal relationship with the treatment.

Note: for example, a fall could be such an event that may-or may not-have an association with a medicine.

4. Definition of adverse drug event

An **adverse drug event (ADE)** is an injury resulting from medical intervention related to a drug. It may be an adverse drug reaction (2.4) or a general event related to medication use.

5. Definition of adverse drug reaction

An **adverse drug reaction** is a response to a drug that is noxious and unintended and that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease or for modifying physiological function (WHO, 1972).

An **adverse drug reaction** is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors (2.7) (EMA [DIR 2001/83/EC Art 1(11)]1).

6. Definition of unexpected adverse reaction

An **unexpected adverse reaction** is an effect not consistent with applicable product information or characteristics of the drug.

7. Definition of a signal

A **signal** is an information that arises from one or multiple sources (incl. observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event, that is judged to be of sufficient likelihood to justify verificatory action.

8. Definition of medication error

A **medication error (ME)** is 'a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient'.[1]

A medication error is any preventable event that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug.

9. Definition of counterfeit product

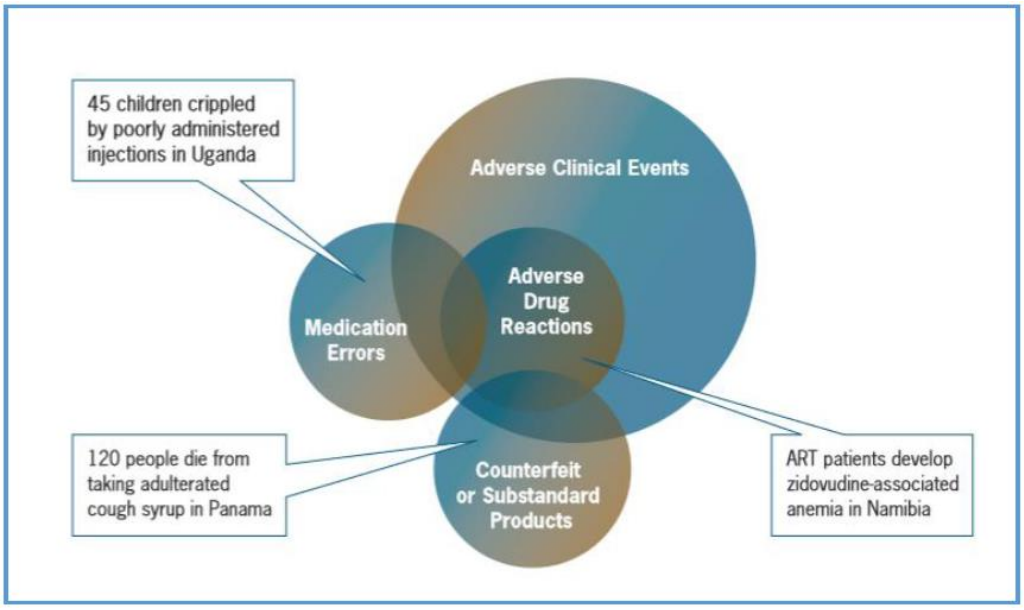
The WHO defines a **counterfeit pharmaceutical product** as a product which is deliberately and fraudulently mislabelled with respect to identity and/or source.[2]

10. The relation between adverse events, adverse drug reactions, medication errors and counterfeit products

An incident may include any irregularity in the process of medication use. It might represent an adverse event, an adverse drug reaction, a medication error or none of these. These categories may **overlap** and it is important to understand their relationship with each other (Figure n. 1). The figure shows some examples.

For example, an insulin dosing error does not necessarily result in hypoglycaemia. This event is defined as "near miss", an error without consequences. In contrast, a medication error (2.7) that triggers hypoglycaemia is defined as an adverse drug reaction (2.4). Similarly, a counterfeit product (2.8) may or may not lead to an adverse drug reaction (2.4).

Figure n. 1 - The relation between adverse events, adverse drug reactions, medication errors and counterfeit products (figure adapted from Br J Clin Pharmacol 2009;67:599-604)



11. Key points

- ✓ Pharmacovigilance is the science related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem.
- ✓ An adverse event is different from an adverse drug reaction. These terms are often confused. An AE is any untoward medical occurrence which does not necessarily have a causal relationship with the treatment. An ADR is any untoward and unintended response to the treatment having a reasonable causal relationship to it.

12. References

1. Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol 2009;67:599-604.
2. WHO. Counterfeit and substandard drugs in Myanmar and Vietnam. World Health Organization, Geneva, Switzerland, 1999.

13. Intermediate Questionnaire

Which is the correct definition of adverse event?

a. an untoward medical occurrence that always has a causal relationship with a treatment

b. an untoward medical occurrence that does not necessarily have a causal relationship with a treatment

c. a failure in the treatment process that always leads to hospitalization

d. a preventable event that occurs during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug

Teaching:

An **adverse drug event (ADE)** is an injury resulting from medical intervention related to a drug. It may be an adverse drug reaction or a general event related to medication use.

What is a signal?

a. an information that suggests a new potentially causal association between a drug and an event

b. an information that implies a proven association between an intervention and an event

c. an epidemiological method used to determine the incidence of ADRs that occur in clinical trials

d. an epidemiological method used to determine the incidence of ADRs that occur in observational studies

Teaching:

A **signal** is an information that arises from one or multiple sources (incl. observations and experiments), which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event, that is judged to be of sufficient likelihood to justify verificatory action.

3. Objectives of pharmacovigilance

1. E-learning objectives

Participants will learn which are the main objectives and methodologies of pharmacovigilance (2.1). After reading this module, they should be able to list also the main advantages and limitations of spontaneous reporting of ADRs.

2. The main objectives of pharmacovigilance:

The main objectives of pharmacovigilance (2.1) are:

- to recognize possible warning signals (2.6) at an early stage when a previously unknown risk is highlighted, when the frequency or severity of a known risk increases, or when a new group of individuals at risk is identified;
- to improve and expand safety information on known adverse drug reactions;
- to identify the risk factors that predispose the appearance of ADRs in the population (age, sex, dosage, concomitant diseases, drug interactions, etc.);
- to estimate the incidence of ADRs;
- to take action to prevent or reduce risks relating to medicinal products.

3. Methodologies in pharmacovigilance

Table n. 2 shows different pharmacovigilance methods.

Table n. 2 - Types of studies used in pharmacovigilance

1. Descriptive approach	▪ Spontaneous reporting of ADR ▪ Case report
2. Analytic approach	▪ Randomized Controlled Trial (RCT) ▪ Case-control study

	▪ Cohort study (e.g. CEM)

1) Descriptive approach

The descriptive approach collects all suspected ADRs sent by healthcare professionals and members of the general public (spontaneous reporting) or derived from cases published in the literature (case reports). This approach lacks of the denominator, i.e. people exposed to the drug who did not present adverse events (2.2).

2) Analytical approach

All these methodologies have the advantage of providing numbers and denominators and therefore they allow to determine an incidence. Also, they allow to evaluate the association between an exposure and an outcome by providing means to quantify the **risk**.
For example, **case-control studies** give the **odds ratio** (OR), whereas **cohort studies** provide the **relative risk** (RR).

Complementary epidemiological methods (cohort and case control studies) required for signal (2.6) validation are yet to be fully developed and applied in the African setting. However, in recognition of some of its known limitations (e.g. under-reporting, limited information obtainable, lack of a denominator), another method of safety surveillance – **cohort event monitoring** (**CEM**, WHO, 2008) – has been introduced to address them and provide prompt answers to issues of safety.

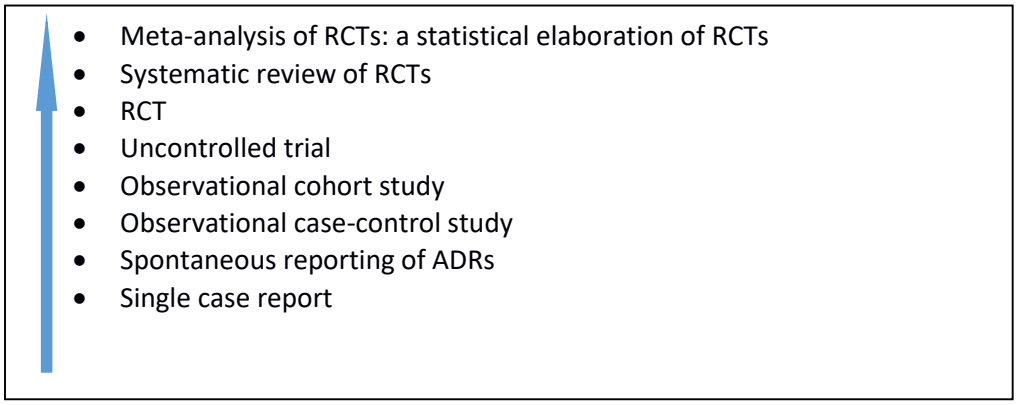
In CEM a group (cohort) of patients is monitored while being treated with a specific medicine (or group of medicines) and all events in a control period before and during treatment shall be recorded.

Examples: CEM has been applied to characterize adverse events (2.2) following the deployment of artemisinin-based combination therapy (ACT) (artemether-lumefantrine, artesunate-amodiaquine) in Ghana, Nigeria, Tanzania and Zimbabwe. The development of the electronic reporting software CemFlow by WHO-UMC has promoted the use of this method[1].

3) The hierarchy of scientific evidences

Figure n. 2 shows the **hierarchy of scientific evidences**

Figure n. 2 - Hierarchy of scientific evidences



4. The spontaneous reporting system

The system of spontaneous reporting was created in the early '60s, following the aforementioned tragedy of thalidomide. **Spontaneous ADR reporting** can be defined as a scheme for collating individual case reports of suspected ADRs, operated for the primary purpose of detecting unknown, potentially seriously harmful effects of drugs.

The spontaneous reporting system allows and requires all healthcare professionals and members of the general public to report suspected adverse drug reactions to their pharmacovigilance unit. The main objective of spontaneous reporting is the early identification of new ADRs.

Table n. 3 shows advantages and disadvantages of the spontaneous reporting.

Table n. 3 - Advantages and disadvantages of the spontaneous reporting

Advantages
• Requires limited economic and organizational resources • Allows simultaneous monitoring of all commercially available drugs • Includes all categories of patients in surveillance • Allows identification of factors predisposing to the occurrence of adverse reactions • Provides early alerts on unusual or unknown reactions, even if rare • Allows comparison of the tolerability profile of drugs of the same therapeutic class
Disadvantages
• Under-reporting of reactions • Difficulties in detecting delayed reactions • The reporting rate is subject to change over time

3.0 5. Under-reporting of ADRs

- ADRs are under-reported in many countries, including African countries.
- **Under-reporting** may delay signal detection and cause underestimation of the size of a problem.
- A systematic review of 37 studies (not African studies) by Hazell and Shakir found a median under-reporting rate of 94% (from 6 to 100%)[2].

The following literature confirms the previous statement:

- Avong and colleagues evaluated the Structured Pharmacovigilance and Training Initiative (SPHAR-TI) model, a training model designed to improve the reporting of ADRs in public health programs treating the human immunodeficiency virus (HIV), tuberculosis (TB) and malaria over a period of 12 months.[3] The SPHAR-TI model was designed to address the challenge of under-reporting of ADRs in Nigeria through capacity building.
- In only just seven months, 3000 individual case study reports (ICSRs) with 100% completeness were submitted, 2937 facility based healthcare workers trained and 46 Pharmacovigilance Committees activated by the participants. Overall, a 273% increase in ICSRs submission to the National Agency for Food and Drug Administration and Control (NAFDAC) was observed. This study showed that an improvement is possible.

6. Key points

- ✓ The main objective of PV is to detect, assess and prevent adverse reactions to drugs.
- ✓ Pharmacovigilance has a descriptive approach and an analytical approach.
- ✓ The spontaneous reporting system allows and requires all healthcare professionals and members of the general public to report suspected adverse drug reactions to their pharmacovigilance unit.
- ✓ The main objective of spontaneous reporting is the early identification of new ADRs.

7. References

1. Ambrose I. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf 2012;3:25-34.
2. Hazell L. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29:385-96.
3. Avong Y. Integrating community pharmacy into community based anti-retroviral therapy program: a pilot

implementation in Abuja, Nigeria. Plos One 2018;DOI:10.1371/journal.pone.0190286.

8. Intermediate Questionnaire

A) Analytical approaches include both case-control studies and case reports

B) Descriptive approaches include both spontaneous reporting of ADR and randomized controlled trials

a. true A, true B

b. true B, false A

c. false A, false B

d. false B, true A

Teaching:

Types of studies used in pharmacovigilance

1. Descriptive approach	▪ Spontaneous reporting of ADR ▪ Case report
2. Analytic approach	▪ Randomized Controlled Trial (RCT) ▪ Case-control study ▪ Cohort study (e.g. CEM)

Which one of these is not a major goal of pharmacovigilance?

a. to improve and expand safety information on known adverse drug reactions

b. to estimate the incidence of ADRs

c. to evaluate the efficacy of new drugs in pre-clinical studies

d. to identify the risk factors that predispose the appearance of ADRs in the population

Teaching:

The main objectives of pharmacovigilance are:

- to recognize possible warning signals at an early stage when a previously unknown risk is highlighted, when the frequency or severity of a known risk increases, or when a new group of individuals at risk is identified;
- to improve and expand safety information on known adverse drug reactions;
- to identify the risk factors that predispose the appearance of ADRs in the population (age, sex, dosage, concomitant diseases, drug interactions, etc.);
- to estimate the incidence of ADRs;
- to take action to prevent or reduce risks relating to medicinal products

4. What's the public health burden of ADRs? Epidemiology of adverse drug reactions

1. E-learning objectives

At the end of this module, participants should be able to provide some examples of ADRs incidence's estimate in different settings and to understand the real public health burden of ADRs.

2. Introduction

The epidemiology of adverse drug reactions is relevant and it is related to their frequency. We can distinguish different settings.

3. ADRs in community

Table n. 4 shows some important studies that have evaluated the **incidence** of **ADRs/ADEs** in **community**. **Most studies agree that 9-10% of patients treated with drugs out of hospital have an** adverse drug reaction (2.4).

Table n. 4 - Studies that have evaluated the incidence of ADRs in non-hospital settings

Country, Author, Journal	Setting	ADRs %	ADEs %	Type of study
Nigeria Alo C African J Med Health Sci 2017;DOI:10.4103/ajmhs.ajmhs_45_16	Ambulatory care		22.0%	Cross-sectional
US Chrischilles E Ann Intern Med 1992;117:634–40	Community-dwelling	10.0%		Survey of a defined population
Italy Leone R Drug Saf 2013;36:267-76	Pharmacy	9.4%		Survey of a defined population
US-Canada Tachè SV Annals Pharmacother 2011;45:977-89	Ambulatory care		9.65% in prospective studies	Systematic review

At the hospital level, a distinction can be made between the reactions that led to hospitalization following the use of drugs in community and those that occurred during hospitalization.

4. ADRs as a cause of hospitalization

Table n. 5 shows_some important studies that have evaluated the **frequency** of **ADRs** as a **cause of hospitalization**. **The frequency in most studies is around 5-8%.**

Table n. 5 - Studies that evaluated the incidence of ADRs as a cause of hospitalization

Country, Author, Journal	ADRs (%) on hospital admissions	ADEs (%)	Type of study
South Africa Mouton JP Medicine 95(19):e3437	8.4%		Cross-sectional survey
11 African countries Mekonnen AB Drugs 2018		8.4%	Systematic review
South Africa, US, Canada, other countries Oscanoa TJ Eu J Clin Pharmacol 2017;DOI:10.1007/s00228-017-2225-3	8.7%		Meta-analysis
England Pirmohamed M BMJ 2004;329:15-9	6.5%		Prospective analysis
Spain, Germany, Australia, other countries (not African countries) Kongkaew C Ann Pharmacother 2008;42:1017-25	5.3%		Systematic review

5. ADRs in hospitals

Table n. 6 shows some relevant studies that have evaluated the **frequency** of **ADRs** in **hospitals**. **The percentage of patients admitted to hospital who experience an ADR is estimated by the majority of studies to be 6-10%.**

Table n. 6 - Studies that have evaluated the incidence of ADRs in hospitals

Country, Author, Journal	ADRs (%)	Type of study
Nigeria Nwani P J Basic Clin Pharmacol 2017;8:245-50	6.7%	Prospective study
Nigeria Aderemi-Williams RI Curr Drug Saf 2015;10:136-44	10.7%	Retrospective study
Europe Bouvy JC Drug Saf 2015;DOI:10.1007/s40264-015-0281-0	10.1%	Review
US Hospitals Lazarou J JAMA 1998;279:1200-5	10.9%	Meta-analysis

6. Fatal ADRs

Drugs can cause serious **ADRs** that can be **fatal**. One of the most important studies (about the incidence of ADRs) is the Lazarou meta-analysis, conducted on hospitalized patients: it estimated ADRs as responsible for 4.6% of deaths and as the fourth cause of death in the United States.[1]

Overall, according to a review of all epidemiological studies quantifying ADRs in a European setting published between January 2000 and September 2014, 0.25% (1 of 400 hospitalized patients) of all patients who are hospitalized due to an ADR will die as a result of the ADR.[2]

The following literature confirms the previous statement:

- In 2017 some authors conducted the first cross-sectional study to determine the mortality rate attributable to ADRs in patients presenting to hospital at Jimma University Specialised Hospital, Ethiopia. Fifteen patients of 1001 (1.5%) died with an ADR. The primary suspected causes of death were drug-induced hepatotoxicity (7, 43.8%) followed by acute kidney injury (4, 25.0%).[3]

- Some authors determined the proportion of deaths in South African medical inpatients attributable to ADRs. They found that 16% of all deaths were ADR-related. Tenofovir, rifampicin and co-trimoxazole were the most commonly implicated drugs.[4]

7. Key points

- ✓ ADRs in community: Most studies agree that 9-10% of patients treated with drugs out of hospital have an adverse drug reaction.
- ✓ ADRs as a cause of hospitalization: the frequency in most studies is around 5-8%.
- ✓ ADRs in hospitals: the percentage of patients admitted to hospital who experience an ADR is estimated by the majority of studies to be 6-10%.
- ✓ Fatal ADRs: up to 0.25% of hospitalized patients can have a fatal ADR

8. References

1. Lazarou J. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200-5.

2. Bouvy J. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf 2015;38:437-53.

3. Angamo M. Mortality from adverse drug reaction-related hospitalizations in south-west Ethiopia: A cross-sectional study. PloS One 2016;12:e0186631.

4. Mouton JP. Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol 2015;80:818-26.

9. Intermediate Questionnaire

According to the scientific literature, which is the percentage of ADRs that lead to hospitalization?

a. 10 %

b. 9 – 10 %

c. 5 – 8 %

d. 6 – 10 %

Teaching
The frequency in most studies is around 5-8%.

Which is the correct estimate of ADRs/ADEs incidence in community?

a. 9 – 10 %

b. 12 - 13 %

c. 2,5 %

d. 0,1 %

Teaching
Most studies agree that 9-10% of patients treated with drugs out of hospital have an adverse drug reaction.

5. How can we prevent ADRs? Patient risk factors for adverse drug reactions

1. Learning objectives

ADRs occurrence depends on many different **factors**, ranging from drug related factors to extrinsic ones. All of these factors also affect ADRs management, so it is important to possess a general understanding of them with respect to the African setting.

By studying this module, participants should be able:

- to distinguish between potential and real drug interactions;
- to explain why age is such an important factor to be taken into consideration when it comes to assess possible ADRs both in children and the elderly;
- to list the key factors of foetal and infant exposure to the drug;

- to provide an example of how drug quality issues can led to ADRs occurrence;
- to define what a counterfeit drug is and which are the steps to be taken to identify such drugs and limit their diffusion;
- to explain the self-medication issue and its impact on the African setting.

2. Introduction

The occurrence of an adverse drug reaction is influenced by multiple factors that can be divided into:

1) **drug related factors**: such as physico-chemical and pharmacokinetic characteristics, dose, frequency, route of administration and duration of therapy;
2) **factors related to the patient**: such as age, pregnancy, allergies or concomitant diseases
3) **additional extrinsic factors**: such as interactions between drugs, use of expired drugs, preservation of the drug, consumption of alcohol, interactions with food and beverages.

We will briefly analyze below the factors that are most involved and most important for the African context.

3. Drug interactions

In Africa drugs are often prescribed irrationally with a potential for causing harm: polypharmacy, inappropriate dosing and coprescription of combinations likely to interact are all prevalent.[1]

There is a distinction between **potential** and **real drug-drug interactions** (DDI):

Potential and real interactions

- **Potential DDI**: It is defined as the occurrence of a potentially harmful combination. In scientific literature, the estimate of the incidence of potential interactions varies greatly, from 6 to 89%.[2-5] A confirm comes from this study: the first study who identified the prevalence of potentially serious drug-drug interactions (DDIs) among an elderly population in the South African private health sector, utilising the Mimica Matanović/Vlahović-Palčevski DDI protocol, estimated potentially serious DDIs in approximately 26% of the prescriptions.[6]
- **Real DDI**: Real drug interaction can be demonstrated in clinical practice. The estimate of elderly patients who are exposed to potential interactions varies between 35 and 60%, but the percentage of these subjects who suffer from clinically significant ADR caused by interactions is 5-15%.[7,8]

Practical Approach:

African countries should also rely on information sources that are readily available to support secondary research on ADEs, especially for HIV-drug interactions (eg.antimalarial and antiretroviral drugs, https://www.hiv-druginteractions.org/ : a free-access interaction checker).[9] For more information read this systematic review on DDI between antiretrovirals and medications used to treat TB, Malaria, Hepatitis B&C and opioid dependence: https://www.who.int/hiv/topics/treatment/drug_drug_interactions_review.pdf

4. Age and Sex

Children and the **elderly** are the two categories of people most susceptible to ADR. We focus mainly on children, because in Africa the population is relatively young.

Children

Children are susceptible to ADRs, because they have not yet fully developed organs and enzyme systems responsible for metabolism with different activities as compared to adults; in addition, off-label drugs are often used for them. In the United States, only a third of the drugs used in children have been adequately studied on them and therefore have specific indications in paediatrics; this percentage is even lower as we approach the neonatal age.[10]

Some authors have reviewed the literature to estimate the incidence of adverse reactions in children.[11] They found that in hospital:

- Nearly 3% (IC 95% 2.6-3.1) is hospitalized due to an adverse reaction;
- Between 0.6 and 16.8% of children have an ADR

The following literature confirms the previous statement:

- Nigeria has a population of 31 million children and the mortality rate is high in children under 5 years (124/1000 live births). Some authors studied ADRs in Nigerian children aged 0-17 years in VigiBase from 2005 to 2012. A total of 297 reports of 473 ADRs in 297 children: ADRs were most frequently reported for anti-retrovirals (74,24%), antibiotics (71,23%) and anti-malarials (60,20%).

- The most frequently reported ADRs were rash (15.2%), fever (10.3%) and pruritus (6.8%). Twenty-one children (7%) died, eight from acute renal failure. Seven of the cases of acute renal failure were associated with contaminated paracetamol/diphenhydramine hydrochloride and herbal medicines used for teething problems. In the majority of cases, the products were contaminated with diethylene glycol. There were 14 cases of Stevens-Johnson syndrome, three of which were fatal.[12]

- Some authors assessed the incidence and nature of ADEs in hospitalized children at a teaching hospital in Ethiopia (Jimma University Specialized Hospital). Fifty eight ADEs were identified with an incidence of 9.2 per 100 admissions, 1.7 per 1000 medication doses and 9.4 per 1000 patient-days.

- One-third of ADEs were preventable; 47% of these were due to errors in the administration stage of medication use process. Regarding the severity of ADEs, 91% caused temporary harms and 9% resulted in permanent harm/death. Anti-infective drugs were the most common medications associated with ADEs.[13]

Practical approach:

South African guidelines on the treatment in pediatry: http://www.kznhealth.gov.za/pharmacy/paediatric-stgs-eml_4thed2017.pdf

Elderly

Elderly people are susceptible to ADRs because of increased exposure to drugs, increased multiple diseases or pharmacodynamic changes. Drug side effects are twice as frequent on average after the age of 65 and 10-20% of these effects lead to hospitalization.[14] A meta-analysis of 68 studies has shown that, in patients over 65 years of age, 16.6% of hospital admissions are caused by ADRs; below 65 years of age the percentage drops to 4.1%.[15]

Aging can have consequences on the action of drugs such as:

- The decrease in the hepatic and renal clearance of some drugs, which determines a change in the dosage of the same;
- The possible alteration of the plasma concentration, of the duration of the action and of the response to a given dose of the drug;
- Alteration of normal homeostatic responses to induced drug changes;
- The osteomuscular loss and the increase of adipose tissue, with consequent modification of the ratio between fat mass and lean mass, determine a tendency to deposit and subsequent release of lipophilic drugs;
- The modification of the permeability of the blood-brain barrier, which can lead to a greater sensitivity towards drugs that act in the central nervous system.

The following literature confirms the previous statement:

- Some authors reviewed the literature from 1990 to 2016 to find interventions towards reducing ADRs among geriatric population in Africa.[16] They included 9 articles: cross-sectional and observational studies involving 2339 (2.1%) elderly outpatient prescriptions, 296 (0.3%) inpatients prescriptions and 109,830 (97.6%) prescriptions from pharmacy database. They found that the polypharmacy and the potential inappropriate prescribing is rife in Africa and it is a major risk factor for ADRs among the African geriatric population.

Practical Approach:

In conclusion, avoiding the use of multiple medicines in the older population is really important. Also, following the Beers criteria (https://dcri.org/beers-criteria-medication-list/) or Stopp and Start for Potentially Inappropriate Medication Use in Older Adults and making sure that only necessary medicines are taken by the patient, it is possible to reduce the risk of ADRs in the elderly.

Sex

Female sex is considered as a risk factor for the development of ADRs.

5. Pregnancy

Every year, numerous drugs with possible effects on the foetus are approved and placed on the market, evaluated only by animal studies, with all the limitations of this methodology. Therefore, only post-marketing epidemiological data or case reports can provide safer indications. Historically, the first observations that associated congenital malformations with exogenous factors were those related to thalidomide.

The key factors of foetal exposure to the drug are:

- the physico-chemical characteristics of the drug (liposolubility, ionization, molecular weight): most drugs pass through the placenta, except those with a really high molecular weight (e.g. heparin is preferable to warfarin, which is teratogenic);
- the extent of the passage through the placenta;
- the concentration of drug that reaches the foetus;
- the distribution to foetal tissues.

The following literature confirms the previous statement:

- Some authors conducted a prospective cross-sectional study to evaluate the incidence of ADRs to artemisinin-based combination therapy among pregnant women in Ibadan, southwestern Nigeria (Adeoyo Maternity Hospital in Ibadan) in 2008. A questionnaire was administered to 140 consented pregnant women and 134 (96%) filled it. Of these 120 (90%) had malaria in their current pregnancy and almost all (96%) took antimalarial drugs. Incidence of experiences of adverse reactions was generally mild, <10% for most of the reactions (we do not have the full text).[17]
- Some authors conducted a cross sectional study in a tertiary care hospital in Ethiopia. A total of 339 women were included in the study: of which 187 (55.2%) had used at least one prescription drug and 162 (52.2%) had used over the counter medications during pregnancy.
- The majority of the medications were antibiotics (42.5%) and analgesics (40.1%). Out of 187 (55.2%) prescription medications used, 51 (15.0%) were obtained without prescribers order. Majority (70.8%) of the women did not have awareness regarding risks associated with self medication. Medications use without prescribers order was common and potentially harmful medications (category D and X) use appeared to be higher in all trimesters.[18]

Practical Approach:

Guideline on pregnancy and drugs: https://www.cdc.gov/pregnancy/meds/treatingfortwo/index.html

6. Breastfeeding

Most of the drugs available on the market are contraindicated during **breastfeeding**. The drugs taken by the mother generally pass into the milk and their concentration differs according to the concentrations in the mother's blood, but also according to the characteristics of the drug.

The key factors of baby exposure to the drug are:

- The lower the molecular weight of a drug, the more likely it will be excreted in breast milk, simply because it is easier to pass through the epithelial cells of the mammary alveoli;

- The spaces between the lactocytes are most permeable in the very first days of breastfeeding and therefore this is the period when the probability of passage is highest;

- Most drugs circulate in the maternal plasma linked to albumin and only the free quota passes into the milk; therefore, drugs with a high protein binding in the maternal plasma almost invariably have low concentrations in the milk.

The following literature confirms the previous statement:

- In resource-limited settings, breastfeeding is essential for children survival. The World Health Organization (WHO) recommend exclusive breastfeeding for the first six months after birth as one of cost-effective interventions in saving children. Prevalence of exclusive breastfeeding (EBF) is low globally (35%), and in sub Saharian Africa ranges between 22 and 33%. The prevalence of EBF is 50% in Tanzania[19] and in Ethiopia is 58%.[20]

- Regarding codeine, the ultra-rapid metaboliser phenotype occurs up to 30% of North Africans. Repeated codeine doses in these women produce significant amounts of morphine. Rapid transfer from maternal plasma to the milk may result in central nervous system depression and potentially infant death. Codeine should be avoided during breastfeeding and alternative analgesics are recommended, such as paracetamol or ibuprofen.[21]

- Azithromycin (AZI) is used for its antibiotic and antimalarial properties in pregnancy. Through the breastfeeding the infant could ingest significant amounts of AZI. Although some infants with bacterial infections may benefit from AZI in breast milk, there is a risk of hypertrophic pyloric stenosis with a number needed to harm of 60.[22]

Practical Approach:

- Breastfeeding and maternal medication: Recommendations for drugs in the eleventh WHO model list of essential drugs. This document has been developed to help the health worker decide whether a mother who is breastfeeding and who needs treatment with drugs can take the necessary medication and still continue breastfeeding safely.[23]

- LactMed (Drugs and Lactation Database): It is a database of the National Library of Medicine's/National Institute of Health included in the Toxnet® network (NLM).[24] It contains information on all drugs to which breastfeeding women may be exposed, provides risk levels for the mother and child and possible adverse effects on the infant, and also provides guidance on complementary and alternative medicine. Access is free and you can connect from your PC, tablet or smartphone. You can download the free app for most smartphones.[25]

- From the Texas Tech University Health Sciences Center, the world's leading research center for medication safety during pregnancy and lactation: https://www.infantrisk.com/:

7. Ethnicity

Pharmacogenetic reactions are typical of individual drug response, in most cases due to pharmacogenetic enzyme deficiencies.

8. Quality issues

In the African setting there have been several reports of problems arising from **defective quality** of medicinal products.

An example is the recurrent contamination of products due to the inadvertent use of diethylene glycol (antifreeze) as diluent. In Nigeria, contamination of acetaminophen by this substance resulted in the death of over 100 children in 1989. Again, in 2009 its use in the preparation of a teething mixture, 'My Pikin', containing acetaminophen and chlorpheniramine, resulted in the death of over 10 children with over 100 cases of acute renal failure.[26]

Furthermore, traditional medicines and herbal remedies are extensively used, with an estimated 80% of the population taking herbal remedies. The use of these herbal remedies raises questions about safety which are yet to be addressed.[26,27]

9. Self-prescription

Self-medication practices, with easy access to both over-the-counter (OTC) and prescription only medicines, are highly prevalent in Africa. In Africa potent medicines are procured from uneducated, uninformed persons who operate in the informal sector and cause untold and devastating harm, the magnitude of which is not really known. The use of 'gift medicines' from family relations and friends within the country or from overseas is a potential source of harmful medicines.[1]

Self-medication in rural Africa has reached a crisis state, as people take anything, and even potentially toxic substances as remedies.

The following literature confirms the previous statement:

- Some authors investigated the self medication profile of the rural people of Cross River and Akwa Ibom States of Southeastern Nigeria. Five hundred and fifty two out of 736 persons which were randomly selected were interviewed with structured questionnaires. The study revealed that 99.4% relied on self medication, while 0.6% consulted physicians. A wide range of substances such as herbs, antibiotics, ash, kerosene, petrol, etc, are used as remedies, and no specific drugs are used for specific ailments, depicting a confusing state of folk medicine in rural Africa.[27]

- Some authors conducted a cross sectional descriptive community survey in Mbeya City in the South-western highlands of Tanzania in 2016. A total of 300 individuals (mean age 35.4 ± 13.4 years) were involved in the study. Prevalence of self-medication with either of the drugs, antibiotic only and antimalarial only was 55.7%, 19.7% and 19.0%, respectively. The main reason that was indicated for the self medication was emergency illness.[28]

Practical Approach:

It is important to ask always the patients, in case of possible ADRs, if they are using any drug that they bought themselves.

10. Counterfeit drugs

Since the late 1980s efforts have been intensified to address the high rate of circulating substandard and **counterfeit medicines (2.8)**. Reports from most African countries, including Kenya, Nigeria and Sierra Leone, underscore the extent of this problem.[29]

WHO published some guidelines for the development of measures to combat counterfeit medicines (2.8) [30] (SF_ (Substandard and Falsified medicinal products_ https://www.who.int/medicines/regulation/ssffc/definitions/en/). Currently, it is estimated that 10-15% of the global drugs are counterfeit. The prevalence is higher in Africa, Asia and Latina America where up to 30-60% of drugs on the market are fake.[31-33]

Practical approach:

- The first step in identifying potential counterfeit drugs (2.8) is the careful visual inspection of the product and its packaging and labelling. A comparison with the authentic drug product is also preferred. Differences in labelling, packaging and in the physical appearance of dosage form indicate a potential counterfeit. Some authors assessed the public awareness (Mkuyuni Ward in Mwanza in Tanzania) and their ability to identify counterfeit antimalarial drugs based on simple observations such as appearance of the drugs, packaging, labelling, and leaflets. The majority of respondents, 163 (55.6%), were able to distinguish between genuine and counterfeit antimalarial drugs.

Figure n. 3 and figure n. 4 show some examples.

Figure n. 3 - Example of sulphadoxine-pyrimethamine 500/25 (genuine and counterfeit)

Sulphadoxine-pyrimethamine 500/25 mg (genuine)

Sulphadoxine-pyrimethamine 500/25 mg (counterfeit)

Figure n. 4 - Example of sulfametopirazine-pyrimethamine 500/25 (genuine and counterfeit)

Sulfametopyrazine-pyrimethamine 500/25 mg (genuine)

Sulfametopyrazine-pyrimethamine 500/25 mg (counterfeit)

- Pharmacists have an integral role in protecting the supply chain from counterfeit drugs (2.8) because of their presumed expertise in drugs, and they are the last point of contact before the patients in the supply chain. This is the quickest and cheapest way to detect counterfeits and, if implemented successfully, can reduce the need for expensive chemical analysis by chromatography and spectroscopy.

- In 2004, the Nigerian National Agency for Food and Drug Administration and Control increased the length of training for community pharmacists with a specific focus on identifying fake drugs using visual aids including the size and shape of tablets and the quality of the printing and holograms on the packaging.[34]

- Obtain medicines from a legitimate pharmacy. All should not buy from open markets, street vendors, or suspicious-looking pharmacies; they should request a receipt when making the purchase.

- Do not buy medicines that are substantially cheaper than the typical price. Although generics are usually less expensive, many counterfeit brand names are sold at prices substantially lower than the normal price for that particular brand.

Useful links:

- CDC: https://wwwnc.cdc.gov/travel/page/counterfeit-medicine

- World Health Organization: www.who.int/mediacentre/factsheets/fs275/en

- WHO guarantee some products, laboratories and ingredients (https://extranet.who.int/prequal/content/prequalified-lists)

11 Key points

- ✓ There is a distinction between potential and real drug-drug interactions.

- ✓ Children and the elderly are the two categories of people most susceptible to ADR.

- ✓ Female sex is considered as a risk factor for the development of ADRs.

- ✓ Most of the drugs available on the market are contraindicated during pregnancy, because they are not studied in pregnant women.

- ✓ Most of the drugs available on the market are contraindicated during breastfeeding, because they are not studied for this condition.

- ✓ In order to avoid self-medication it is important to ask always the patients, in case of possible ADRs, if they are using any drug that they bought themselves.

- ✓ The prevalence of counterfeit drugs (2.8) is higher in Africa. A practical approach can help HCP in order to avoid it.

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13. Intermediate Questionnaire

Which of these factors does not affect drug action in the elderly?

a. the modification of the blood-brain barrier permeability

b. the increase of adipose tissue

c. the lack of fully developed enzyme systems

d. the alteration of normal homeostatic responses to changes induced by drugs

Teaching:

Aging can have consequences on the action of drugs such as:

- The decrease in the hepatic and renal clearance of some drugs, which determines a change in the dosage of the same;
- The possible alteration of the plasma concentration, of the duration of the action and of the response to a given dose of the drug;
- Alteration of normal homeostatic responses to induced drug changes;
- The osteomuscular loss and the increase of adipose tissue, with consequent modification of the ratio between fat mass and lean mass, determine a tendency to deposit and subsequent release of lipophilic drugs;
- The modification of the permeability of the blood-brain barrier, which can lead to a greater sensitivity towards drugs that act in the central nervous system.

Counterfeit drugs:

a. are products approved by the Tanzania Food and Drug Administration but commonly associated with a high incidence of ADRs

b. are products which are deliberately and fraudulently mislabelled with respect to identity and/or source

c. should be prescribed by healthcare professionals when no alternatives are available

d. should be prescribed by healthcare professionals in place of generics

Teaching:
Counterfeit drugs are products which are deliberately and fraudulently mislabelled with respect to identity and/or source

6. How to recognize ADRs

1. E-learning objectives

Here a description of a practical approach to recognize possible drug-related ADRs is given.
By learning the contents of this short module, participants will gain an insight into ADR identification and assessment from a practical point of view.

2. Introduction

It is not an easy task to determine whether a patient is experiencing an adverse effect from a drug. This difficulty may partly explain why many ADRs are never recognized as adverse events (2.2). Patients who are experiencing an adverse drug effect rarely think the problem was caused by a drug that they are taking.
Here a description of a practical approach to **recognize possible** drug-related **ADRs** is given.

Practical Approach:

the following step-wise approach may be helpful in assessing possible drug-related ADRs:

1. Consider always the possibility that a drug may be associated with an exacerbation of a patient's condition or with the emergence of a new medical problem. If you don't even look, you won't find them.

2. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose suggested.

3. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient.

4. Determine the time interval between the beginning of drug treatment and the onset of the event.

5. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events (2.2).

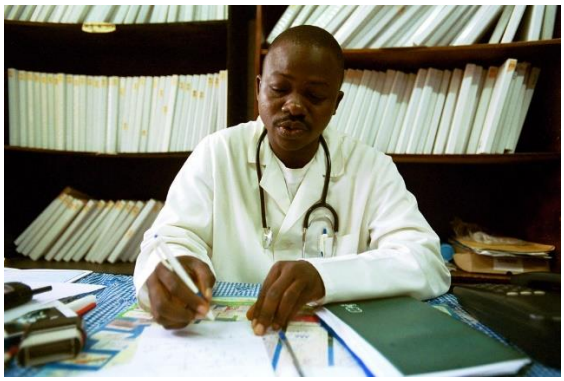
6. Analyse the alternative causes (other than the drug) that could on their own have caused the reaction.

7. Use relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The National Pharmacovigilance Centre and Drug Information Centres are very important resources for obtaining information on ADR. The manufacturer of the drug can also be a resource to consult.

8. The most common ADR targets are the skin and the gastrointestinal tract.

9. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the National ADR Centre.

10. It is important to recognize the ADR as soon as possible to avoid the prescription cascade. It is the process whereby the side effects of drugs are misdiagnosed as symptoms of another problem, resulting in further prescriptions and further side effects. An example is the prescription of a proton pump inhibitor to reduce gastrointestinal adverse effects associated with non-steroidal anti-inflammatory drugs (NSAIDs).



3. Key points

- ✓ It is not an easy task to determine whether a patient is experiencing an adverse effect from a drug.
- ✓ A practical approach may be helpful in assessing possible drug-related ADRs.

4. References

1. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action (2002)

5. Intermediate Questionnaire

In order to identify possible ADRs, a healthcare professional should:

a. verify that the onset of the suspected ADR occurred before the drug was taken

b. verify that the onset of the suspected ADR occurred after the drug was taken

c. evaluate the suspected ADR after increasing the dose of the drug

d. evaluate the suspected ADR without suspending the treatment

Teaching:

In order to identify possible ADRs, a healthcare professional should verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient.

A) In general, the most common ADRs targets are the cardiovascular and the immune system

B) Drug interactions represent an alternative cause of ADRs

a. A false, B false

b. A true, B false

c. A true, B true

d. A false, B true

Teaching:

The most common ADR targets are the skin and the gastrointestinal tract.
Drug interactions represent an alternative cause of ADRs

7. Classifications of ADRs and practical management

1. E-learning objectives

This paragraph shows the **classification** of ADRs and some practical **suggestions** to **manage** the ADRs. Please consider that decisions are made by considering:

- seriousness / severity of ADR;
- seriousness of disease;
- benefit / harm assessment.

Participants will learn how to classify ADRs according to their mechanism, their nature and their frequency. Moreover, the module will provide them with some practical examples of different types ADRS and how to manage them.

2. Classification of ADRs by mechanism

Adverse drug reactions (2.4) can be distinguished according to their mechanism, as shown in Table n. 7.

Table n. 7 - Classification of ADRs by mechanism

ADR	Characteristics	Examples	ADR Management
Side effects	• They are linked to the pharmacological effect of the drug • They are mainly due to the distribution of the drug in the body • Also manifest themselves at therapeutic doses	Nitrate headache	Consider: **1** **2** Dose reduction **3** An alternative drug **4** To stop unnecessary drugs
Toxic effects	• They are due to the toxicity of the drug • They appear at overdoses, but may also occur at therapeutic doses	Hepatic failure from acetaminophen	Consider: **1** **2** Dose reduction **3** An alternative drug **4** To stop unnecessary drugs

Immune mediated reactions	• Type I, Type II, Type III and Type IV	Anaphylactic shock from penicillin	Consider: **2** **3** An alternative drug **4** To stop unnecessary drugs
Pharmacogenetic reactions	• They can modify pharmacokinetics (hyperactivity) or tissue response (idiosyncrasy) to drugs • The main causes are genetic polymorphisms at the level of the cytochrome P450 system	African genetic diversity	Consider: **1** To continue treatment and treat symptoms of reaction if necessary **2** Dose reduction **3** An alternative drug **4** To stop unnecessary drugs
Drug addiction	• Uncontrollable desire to take a drug •	Dependence on opioids, benzodiazepines	Consider: Try to choose drug with no or low drug addiction effects
Teratogenic effects	• Capacity of a drug administered to a pregnant woman to cause malformations in the foetus • The type of malformation depends on the period of exposure and the teratogenic properties of the drug	Tetracycline bone malformations	Consider: Try to choose drug with no or low teratogenic risk

The correct classification of an ADR has important clinical implications, especially with regard to future exposure or avoidance of the drug. For example, in the case of immune mediate reactions, avoidance of the same drug and structurally-related drugs in any dose is required. In certain circumstances, the risk of adverse drug reaction (2.4) can also be mitigated by altering the dose or formulation, or by the administration of other medications.

Side effects

Side effects are due to the mechanism of action of the drug and are related to the dose administered. They occur at normal therapeutic doses in organs or organ systems other than those desired. From a clinicians' perspective it could be possible to low the dose to avoid these types of ADRs.

Toxic effects

Toxic effects are an expression of the drug's toxicity and appear at high doses, but may also occur at therapeutic doses in particular clinical conditions (example hepatic failure from acetaminophen).

Immune mediated reactions

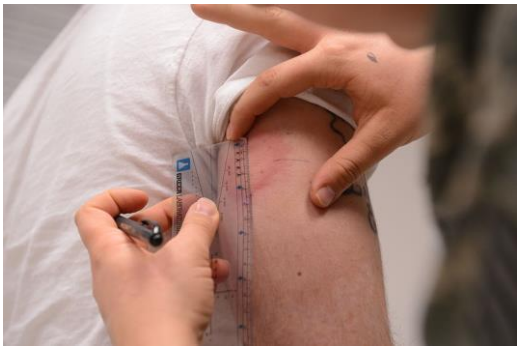
Allergic (or hypersensitivity) ADRs are immune mediated and independent of the mechanisms of action and dose of the drug. Based on the immunological mechanism involved, allergic reactions are classically divided into four general categories:

- type I or anaphylactic, mediated by IgE antibodies. The main targets of this type of reactions are the skin (urticaria or dermatitis), the respiratory system (asthma) and blood vessels (anaphylactic shock), (example: anaphylactic shock due to penicillin);

- type II or cytolytic, mediated by IgG and IgM antibodies with complement activation. The main targets are blood cells; example: Trasfusional reactions due to incompatibility ABO or Rh factors, haemolytic anemia due to cephaloporines, metyldopa;

- type III, mediated by IgG with the formation of antigen-antibody complexes that de (osit in the endothelium, where develops an inflammatory response called serum disease. The symptoms are urticaria-like skin reactions, arthralgia or arthritis, lymphadenopathy and fever; Toxic Epidermolysis Necrotic due to sulfonamides, phenytoin;

- type IV or delayed, mediated by T lymphocytes and sensitized macrophages. Contact allergy (latex, metals, tubercolin test).



Pharmacogenetic reactions

Pharmacogenetic reactions are typical of individual drug response, in most cases due to pharmacogenetic enzyme deficiencies. A relevant role, in the context of the ADRs on genetic base, is played by the genetic polymorphisms of the cytochrome enzymatic system P450 (CYP). Genetic diversity in CYP is greater in Africa than in other continental populations.[1]

The following literature confirms the previous statement:

- Some authors identified CYP alleles of potential clinical relevance with a marked difference in distribution in Africa, compared with Asian and Caucasian populations. These were CYP2B6*6, CYP2C8*2, CYP2D6*3, CYP2D6*17, CYP2D6*29, CYP3A5*6, and CYP3A5*7.[1]

- Patients who are CYP2D6 ultrarapid metabolizers should avoid codeine use due to potential for morphine toxicity. Roughly 1-10% of whites of Caucasians are CYP2D6 ultra-rapid metabolizers. In contrast, from 16 to 28% in North Africans, Ethiopians, and Arabs are ultra-rapid metabolizers.[2]

- The work by Parikh and colleagues highlighted the role of common polymorphisms in the cytochrome P450 CYP2C8 impairing amodiaquine metabolism and its implications for malaria treatment in Africa. Metabolism of the antimalarial drug amodiaquine into its primary metabolite, N-desethylamodiaquine, is mediated by CYP2C8. The variant most common in Africans, CYP2C8(*)2, showed defective metabolism of amodiaquine and CYP2C8(*)3 had markedly decreased activity. They studied the frequency of CYP2C8 variants in 275 malaria-infected patients in Burkina Faso, the metabolism of amodiaquine by CYP2C8 variants, and the impact of other drugs on amodiaquine metabolism. The metabolism of amodiaquine has been characterized in studies using human liver microsomes and recombinant enzymes. No evidence was seen for influence of CYP2C8 genotype on amodiaquine efficacy or toxicity, but sample size limited these assessments.[3]
- Variations in the N-acetyltransferase (*NAT2*) gene among different populations could affect the metabolism and disposition of isoniazid (INH)*.

Practical Approach:

Useful link to detect possible interactions at the level of cytochrome P450 metabolism: https://drug-interactions.medicine.iu.edu/Main-Table.aspx

Drug addiction

- *Psychic dependence*: dependence on a substance that is characterized as a compulsive and unstoppable desire to take it.

- *Physical dependence*: manifested through the withdrawal syndrome that appears when you no longer take the drug. Withdrawal syndrome occurs after a certain period of time from the last use (which varies according to the type of drug) and is characterized by a series of unpleasant and even serious events.
- *Tolerance*: the need to increase the dose to achieve the desired effect.

Teratogenic effects

A drug is defined as teratogenic if it has the ability to cause malformations, both macroscopic and functional, in the foetus. There are mainly two types of teratogenic risk classification:

- FDA (Food and Drug Administration) Classification: the most used and restrictive;
- ADEC (Australian Drug Evaluation Committee) Classification.

3. Classification of ADRs according to their nature

ADRs were classified by Rawlins and Thompson (see Table n. 8) into reactions of type A (dependent and predictable doses) and type B (dose-independent and unpredictable).[4]

Table n. 8 - Classification of adverse drug reactions (ADRs) according to their nature

ADRs	Distinctive features	Some examples	ADR Management
Type A (Augmented)	• Dose-related • Mechanism of action-related • Common • Predictable • Low mortality • Generally discovered before commercialization	• Hepatotoxicity from anti-tubercular drugs • The negative effect of tenofovir on bone mineral density, which may increase fracture risk	Consider: **1** To continue treatment and treat symptoms of reaction if necessary **2** Dose reduction **3** An alternative drug **4** To stop unnecessary drugs Management
Type B (Bizarre)	• Not dose related • Not related to mechanism of action • Uncommon • Unpredictable • High (relative) mortality • Generally discovered after commercialization	• Anaphylactic shock from amoxicillin + clavulanic acid	Consider: **1** **2** **3** An alternative drug **4** To stop unnecessary drugs

Adverse reactions of type A

- They are the most frequent ones (25 to 40% of patients, up to 100% in the case of antineoplastics).
- They are common, dose and mechanism of action related, largely predictable and sometimes avoidable using lower dosages for the individual patient.
- They have high incidence and morbidity, but rarely result in death.
- Generally discovered before commercialization.

Practical Approach: A patient being treated with furosemide) develops hypokalemia. By reducing the dosage of the drug and with a potassium supplementation the potassium levels return to normal, and the patient can continue to use the same drug.

Adverse reactions of type B

- They are often allergic or idiosyncratic, occur only in a minority of patients and are usually unexpected and unpredictable.

- Except for the immediate hypersensitivity reaction (anaphylaxis), such reactions usually appear at least five days after the start of treatment, but there is no maximum time limit and most of them occur within twelve weeks.

- They are usually severe, unrelated to the dose, independent of the pharmacological action and generally discovered after commercialization. Some pharmacogenetic reactions recognise a predisposition to a congenital error of metabolism or to an acquired deficiency of an enzyme, resulting in an abnormal metabolic pathway or accumulation of toxic metabolites.

Practical Approach: A patient with a respiratory infection is treated with amoxicillin 1 g x 2 per day. After 4 days he begins to complain of diffuse itching, urticaria, edema of the lips and eyelids. This is an allergic reaction to amoxicillin, and it is not a dose dependent reaction. The patient must stop therapy, switch to another class of antibiotics (usually macrolides), and no longer take penicillins, because of the risk of much greater reactions such as anaphylactic shock.

4. Classification of adverse reactions by frequency

The **frequency** of ADRs, together with severity, is in fact a crucial element in establishing the benefit/risk ratio of a drug. The suggested scale for this type of classification is that proposed by the Council for International Organizations of Medical Sciences (see Table n. 9).

Table n. 9 - Council for International Organizations of Medical Sciences Scale for the frequency of ADRs

ADRs frequency	Case no./Exposure no.	Examples
Very frequent	>1/10	Gastrointestinal NSAID disorders
Frequent	>1/100 - <1/10	Myalgia from statins
Not frequent (occasional)	>1/1.000 - <1/100	Myopathy from statins
Rare	>1/10.000 - <1/1.000	Rhabdomyolysis from statins, hearing loss from fluoroquinolones
Very rare	<1/10.000	Achilles tendon rupture from fluoroquinolones, mandibular osteonecrosis from biphosphonates

5. Classification of adverse reactions by seriousness and severity

- **Serious**: Any untoward medical occurrence that, at any dose, results in death; is life threatening; requires inpatient hospitalization or prolongs current hospitalization; results in persistent or significant disability, incapacity, or congenital abnormality. This contrasts with severe.

- **Severity**: The intensity of an adverse reaction. An ADR can also be assessed by its intensity as mild, moderate or relevant.

6. Classification of ADRs according to their preventability/avoidability

In Africa medication errors remain a significant drug related problem. This has been highlighted by findings in Morocco[5,6] and it is yet to be fully evaluated in the African setting.[7] Prescribing errors are one of the biggest problems among medication errors.

How many ADRs can be avoided, i.e. caused by medication errors? According to the literature, more than 40% of ADRs are preventable (see Table n. 10).

Table n. 10 - Percentage of preventable ADRs

Country, Author, Journal	%
South-Africa	45.0

Mouton JP Medicine 2016;DOI:10.1097/MD.0000000000003437	
Netherland Leendertse AJ Arch Intern Med 2008;DOI:10.1001/archinternmed.2008.3	46.5
US, Canada, Germany, Spain, other countries Hakkarainen K PLoS One 2012;DOI:10.1371/journal.pone.0033236	45.0
France, Italy, Canada, Australia, other countries Winterstein AG Ann Pharmacother 2002;36:1238-48	59.0
England Pirmohamed M BMJ 2004;329:15-9	72.0

7. Key points

- ✓ Adverse drug reactions can be distinguished according to their mechanism into side effects, toxic effects, immune mediated reactions, pharmacogenetic reactions, drug addiction and teratogenic effects.
- ✓ Adverse drug reactions can be distinguished according to their nature into Type A and Type B reactions.
- ✓ Adverse drug reactions can be distinguished according to their frequency into very frequent, frequent not frequent, rare and very rare.
- ✓ ADR can be distinguished according to their seriousness and severity.
- ✓ ADR can be distinguished according to their preventability/avoidability. According to the literature, more than 40% of ADRs are preventable

8. References

1. Rajman I. African genetic diversity: implications for cytochrome P450-mediated drug metabolism and drug development. EBioMedicine 2017;17:67-74.
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3. Parikh S. Amodiaquine metabolism is impaired by common polymorphisms in CYP2C8: implications for malaria treatment in Africa. Clin Pharmacol Ther 2007;82:197-203.
4. Rawlins MD. Clinical pharmacology. Adverse reactions to drugs. BMJ 1981;282:974-6.
5. Ali L. Detecting medication errors in pharmacovigilance database: capacities and limits. Int J Risk Saf Med 2007;19:1-18.
6. Bencheikh R. Medication errors: pharmacovigilance centres in detection and prevention. Br J Clin Pharmacol 2009;67:687-90.
7. Ambrose I. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf 2012;3:25-34.

9. Intermediate Questionnaire

Hepatic failure due to acetaminophen is an example of:

a. toxic effect

b. pharmacogenetic reaction

c. teratogenic effect

d. immune-mediated reaction

Type B adverse reactions are:

a. dose-related adverse drug reactions

b. the most frequent type of adverse drug reactions

c. often allergic adverse drug reactions

d. always pharmacogenetic adverse drug reactions

Teaching:

Hepatic failure due to acetaminophen is an example of toxic effect.

Type B adverse reactions are often allergic adverse drug reactions

8. Pharmacovigilance in Africa

1. E-learning objectives

This module focuses on how the pharmacovigilance system is organized and how it operates in the African setting.

A description of the WHO Programme for International Drug Monitoring is given , as well as the list of African countries that have joined the Programme. Moreover, Vigiflow and Vigibase, two essential tools of global pharmacovigilance are introduced. The module ends with two charts that show the contribution of African countries to global pharmacovigilance in terms of submitted reports.

By reading this module, participants will gain insights into both African and global pharmacovigilance, learning more about the main features of the African reports.

2. WHO Programme for International Drug Monitoring

Established in 1968 after the Thalidomide Disaster (1961) the WHO Programme for International Drug Monitoring (PIDM) provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals. Thereafter, in 1978, the Programme and the overall operational responsibilities were transferred to Sweden with the establishment of PIDM in Uppsala, Sweden.

The programme consists now of a three-part network:

1. National pharmacovigilance centres from WHO member countries are responsible for case reports sent to the WHO ICSR (Individual Case Safety Reports) database, called Vigibase (managed by the Uppsala Monitoring Centre (UMC) in Sweden). In September 2018, there were over 18 million reports of adverse reactions in VigiBase.

2. UMC oversees the WHO programme operations, including:

    - collecting, assessing and communicating information from member countries about the benefits, harm, effectiveness and risks of drugs;

- collaborating with member countries in the development and practice of pharmacovigilance (2.1);

- alerting the National Regulatory Authorities (NRAs) of member countries about potential drug safety problems via the WHO signal process.

3. WHO headquarters in Geneva, Switzerland is responsible for policy issues.

As of December 2018, 134 countries have joined the WHO PIDM, and in addition, 29 associate members are awaiting full membership. The pharmacovigilance system in African countries is based essentially on spontaneous reporting. This has been facilitated by the introduction of Vigiflow (a web-based ICSR management system), which enables online transmission of ICSRs to Vigibase, obviating the need for a local database. In 2017 Ethiopia was the first country to go alive with Vigiflow.

Other tools, such as Vigilyze, provide techonological expertise to African Countries that otherwise would not have been able to have the appropriate tools to manage their safety data. However, there are some obstacles such as the mainly inability to recognize ADRs, ignorance of the reporting requirements, lack of reporting forms (etc...)[1].

Table n. 11 shows Full African member countries of the World Health Organization International Drug Monitoring Programme (6 th December, 2018).

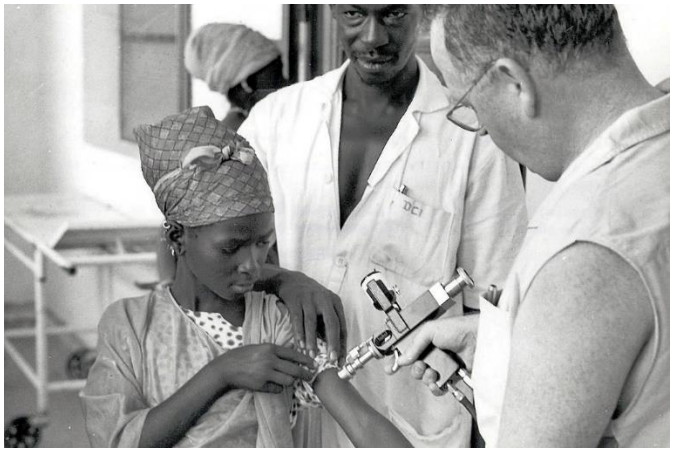
Table n. 11 - African countries full member of the World Health Organization international drug monitoring programme (6 th December, 2018)

N.	Country	Year of entry	N. of reports
01	Morocco	1992	
02	South Africa	1992	
03	Tunisia	1993	
04	Tanzania	1993	
05	Zimbabwe	1998	
06	Egypt	2001	
07	Ghana	2001	
08	Nigeria	2004	
09	Mozambique	2005	
10	Togo	2007	
11	Uganda	2007	
12	Ethiopia	2008	
13	Namibia	2008	
14	Sierra Leone	2008	
15	Sudan	2008	
16	Botswana	2009	
17	Madagascar	2009	
18	Senegal	2009	
19	Kenya	2010	
20	Zambia	2010	
21	Cameroon	2010	
22	Cote D'Ivoire	2010	
23	Dem. Rep. Congo	2010	
24	Burkina Faso	2010	
25	Benin	2011	
26	Mali	2011	
27	Cabo Verde	2012	

28	Eritrea	2012	
29	Niger	2012	
30	Guinea	2013	
31	Rwanda	2013	
32	Liberia	2013	
33	Angola	2013	
34	Mauritius	2014	
35	Eswatini	2015	
36	Chad	2018	

3. African Chapter of ISop (ASoP)

It was launched in November 2009 during the 32nd WHO meeting in Rabat (Marocco). It includes 16 African nations (https://isoponline.org/chapters/africa/). Its main aims are to promote and enhance PV in African Countries and to develop educational programs in pharmacovigilance.



4. African Data from Vigibase

To February 2019 Vigibase contained about 18 milion of reports. African States reported about 163.266 report (0.9%) (February 2019). The contribution is small within the global database. In particular, Nigeria reported about 10,000, Tanzania about 2000, Ethiopia about 1200, Swaziland about 30. The state that mainly contributes is South Africa. To February 2019 it has sent around 50,000 reports, followed by Morocco (around 26000) and Egypt (around 25,000). With regard to the 163.266 reports we can say that:

- they were reported especially from 2008 to 2018;
- most refer to women (56.8%) and to the age group between 18 and 44 (37.6%);
- most reported drugs were lamivudine, sulfamethoxazole/trimethoprim and nevirapine as reported in figure n. 5;
- ADRs most frequently reported were skin and subcutaneous tissue disorders followed by general disorders and administration site conditions as reported in figure n. 6.

Figure n. 5 - Top reported substances of 163.266 reports

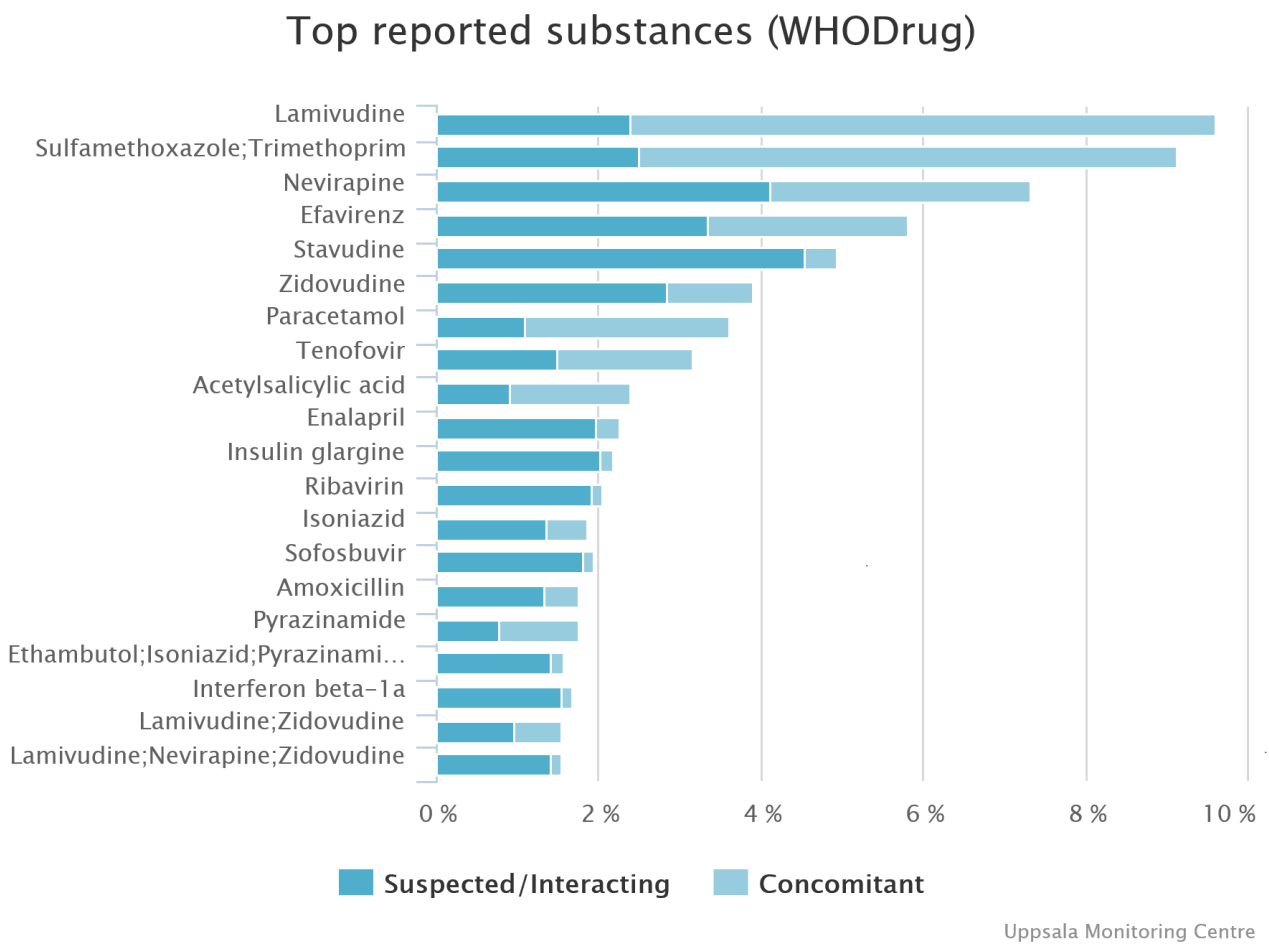
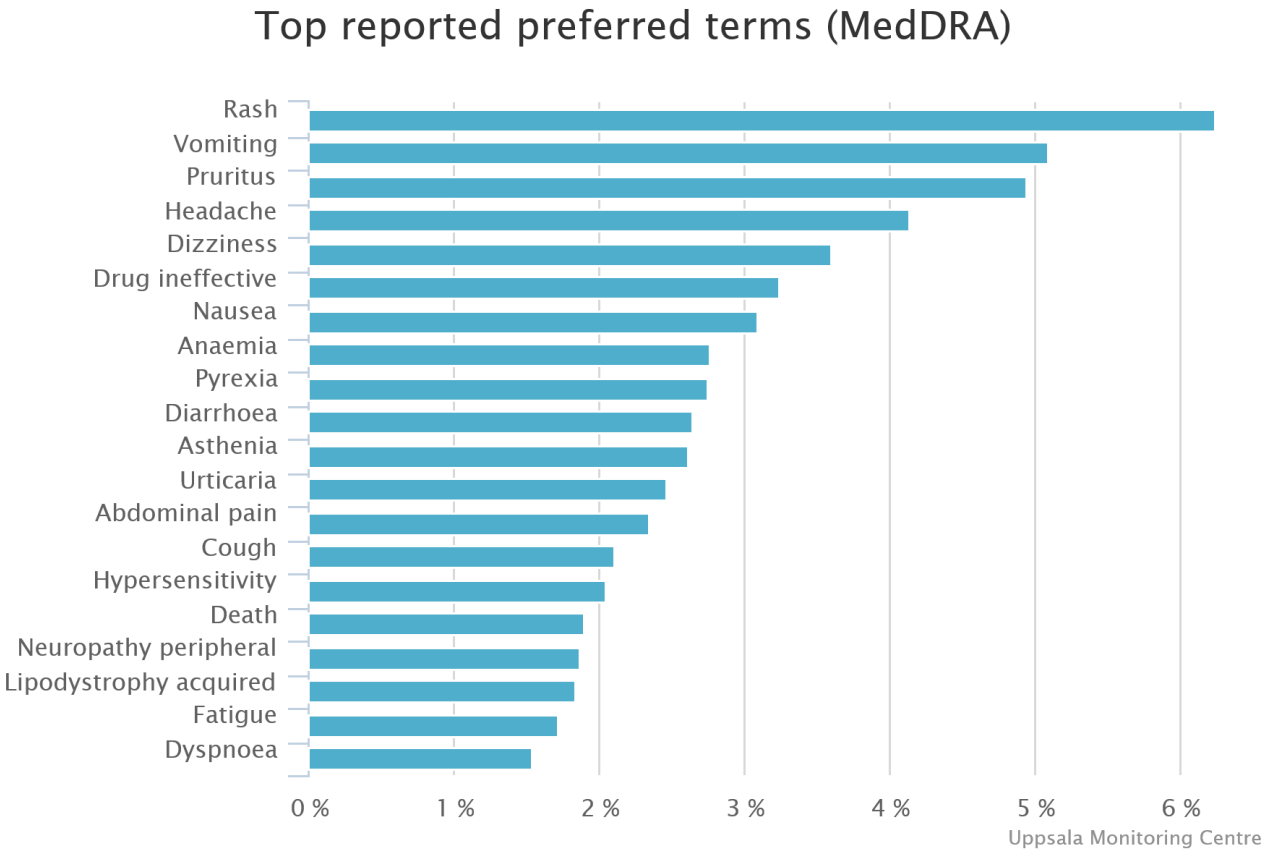


Figure n. 6 - Top reported preferred terms of 163.266 reports



5. Key points

- ✓ WHO Programme for International Drug Monitoring provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals (2.6).
- ✓ Tanzania, Nigeria, Ethiopia and Eswatini are full members of the WHO international drug monitoring programme.
- ✓ African Chapter of ISoP. It includes 16 African nations. Its main aims are to promote and enhance PV in African Countries.
- ✓ To February 2019 Vigibase contained about 18 milion of reports. African States reported about 163.266 report (0.9%).

6. References

1. Ambrose I. Specific features of medicines safety and pharmacovigilance in Africa. Ther Adv Drug Saf 2012;3:25-34

7. Intermediate Questionnaire

What is Vigibase?

a. a network of pharmacovigilance centers established in Africa

b. a database of individual case safety reports managed by Uppsala Monitoring Centre

c. a WHO international programme that is aimed at monitoring drug safety worldwide

d. a newly developed methodology for identifying rare ADRs

Teaching:

Established in 1968 after the Thalidomide Disaster (1961) the WHO Programme for International Drug Monitoring (PIDM) provides a forum for WHO Member States to collaborate in the monitoring of drug safety, and notably, the identification and analysis of new adverse reaction signals. Thereafter, in 1978, the Programme and the overall operational responsibilities were transferred to Sweden with the establishment of PIDM in Uppsala, Sweden. Vigibase is a database of individual case safety reports managed by Uppsala Monitoring Centre

The WHO Programme for International Drug Monitoring:

a. counts 110 member countries

b. counts 134 member countries

c. does not include Ethiopia

d. does not include Tanzania

Teaching

As of December 2018, 134 countries have joined the WHO PIDM, and in addition, 29 associate members are awaiting full membership. The pharmacovigilance system in African countries is based essentially on spontaneous reporting. This has been facilitated by the introduction of Vigiflow (a web-based ICSR management system), which enables online transmission of ICSRs to Vigibase, obviating the need for a local database. In 2017 Ethiopia was the first country to go alive with Vigiflow.