MODULE I

The Importance of Pharmacovigilance

This is a joined presentation between NPC and SAHPRA

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28 November 2023

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Objectives

- Explain the historical background of pharmacovigilance
- Explain and understand what pharmacovigilance means
- Explain why pharmacovigilance is important

Objective 1

- Explain the historical background of pharmacovigilance

Historical Evolution of Pharmacovigilance

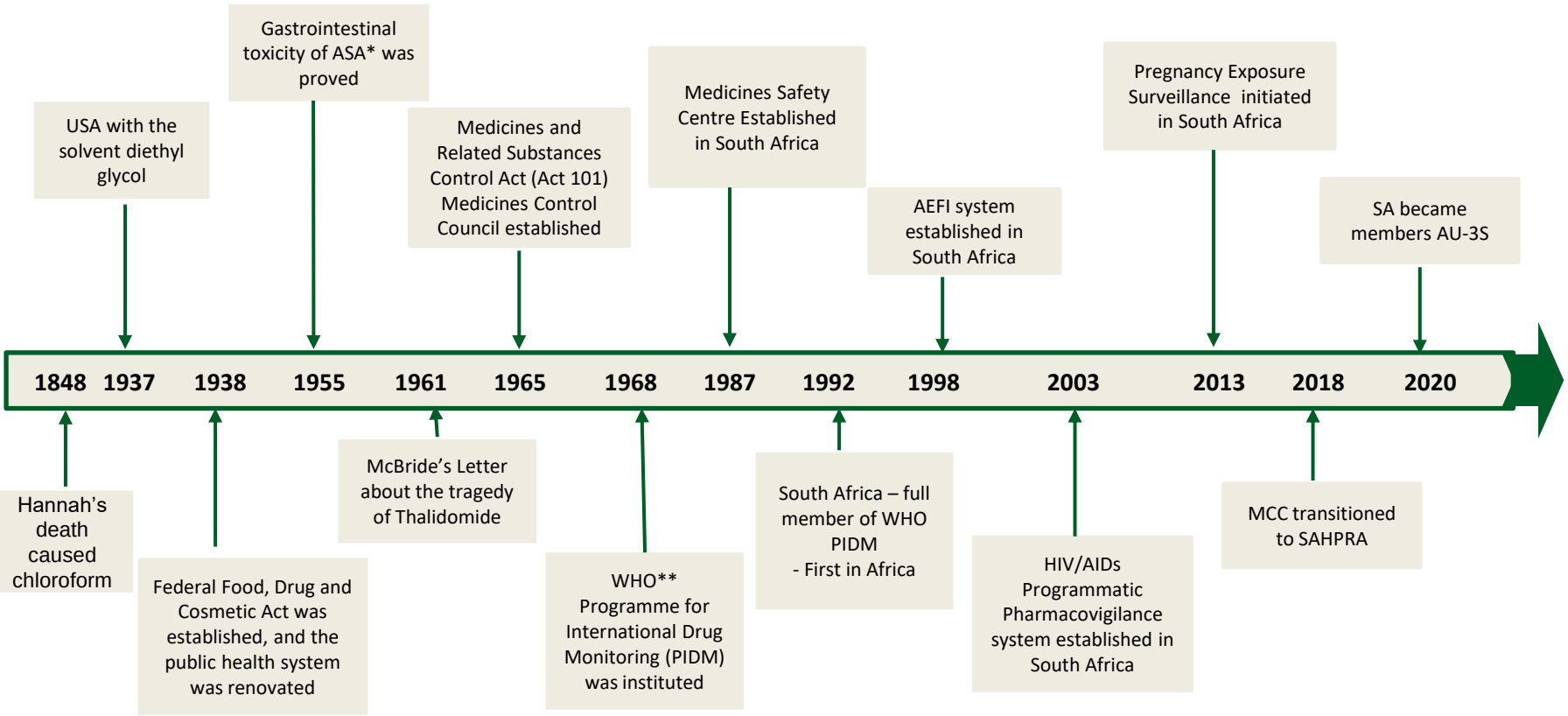
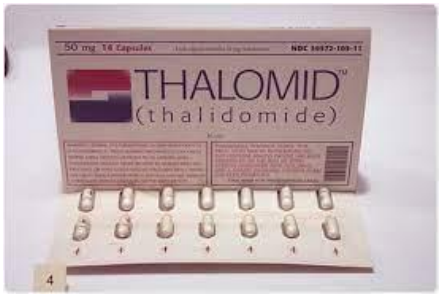


Figure 1: Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; WHO: World Health Organisation; MCC: Medicine Control Council; AU-3S: African Union – Smart Safety Surveillance

Adapted from Fornasier et al., (2018:745)

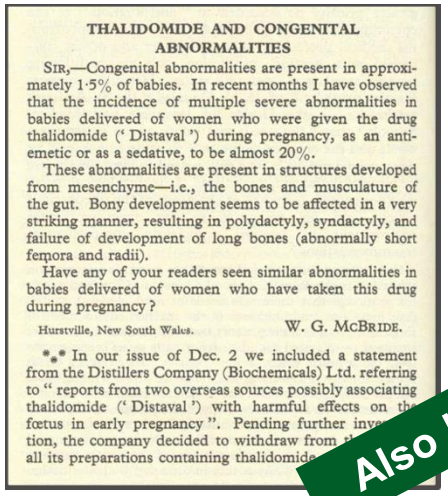
The Thalidomide Tragedy



Tranquilizer launched in 1957

Used off- label to treat nausea in pregnant women

1959- First reports of birth defects



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.

13 reports of birth defects – 1961

10,000 infants affected
only 50% survived.
Not detected during clinical trials and before launch

Also highlighted the importance of regulating medicines across the globe!

1963 – World Health Assembly resolution – systemic collection of serious adverse drug reactions (ADRs)

In 1968, the WHO established its Programme for International Drug Monitoring (PIDM)

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Response to thalidomide!

Objective II

Explain and understand what pharmacovigilance means

What is Pharmacovigilance?

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding & prevention of suspected adverse effects (adverse drug reactions) or any other drug-related problems.

The Importance of Pharmacovigilance: WHO 2002

Understanding Pharmacovigilance

Detection

- Spontaneous Reporting
- Diagnosis of ADRs
- Signals of new or previously poorly understood ADRs
- Other surveillance and research methods (cohort, case control, PEM, record linkage studies, registries etc)

Assessment

- Research – signal strengthening and signal validation
- Causality Assessment, severity, extent of the problem, preventability
- Risk factors, biological mechanism, public health impact

Understanding

- Education and training
- Determine the cause of the ADR
- Clarify the risk factors related to the ADR.

Prevention

- Rational use of medicines
- Communication and training
- Health system changes
- Education

Drug-related problems….

Understanding Pharmacovigilance

Abuse/misuse & overdose

Adverse drug events

Poor access to safer and more effective medicines

Potentially unsafe treatment policies

Drug-related problems

Environmental contamination of pharmaceuticals

Counterfeit or substandard medicines

Inappropriate storage, handling, use and disposal of medicines

Medication errors and drug-interactions

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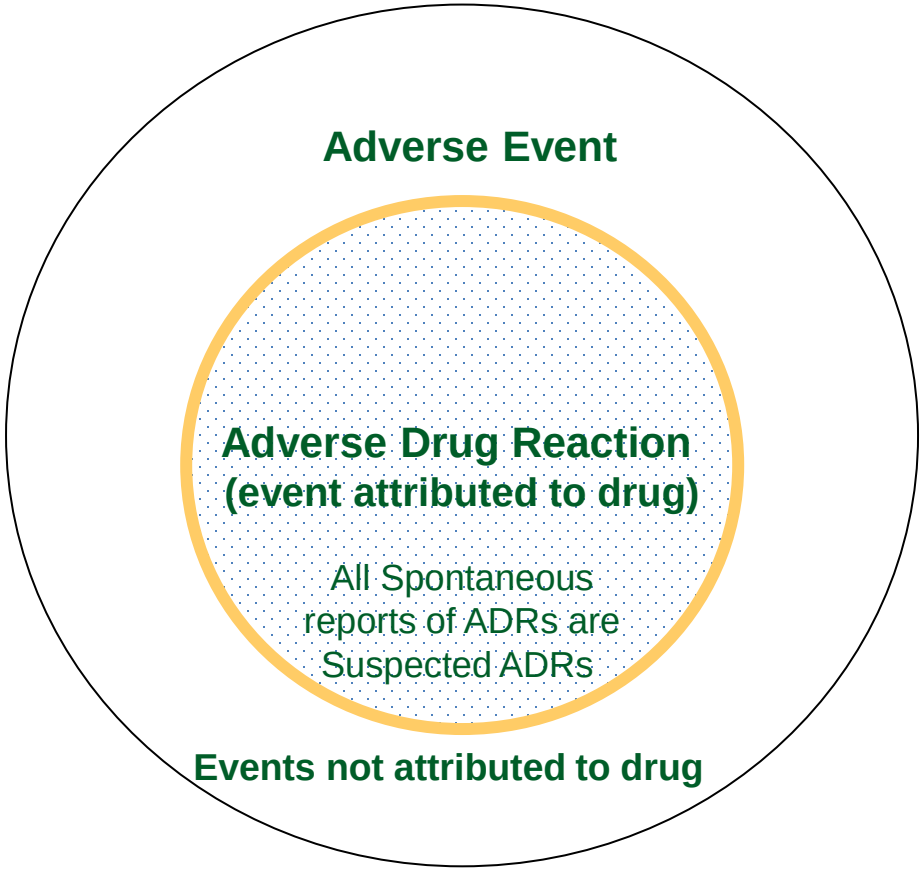
Pharmacovigilance Terminology

Adverse Event:
An untoward medical occurrence which does not necessarily have to have a causal relationship with the treatment.

Adverse Drug Reaction (ADR)
A noxious and unintended response to a medicine, including lack of efficacy, and which occurs at doses normally used in man and which can also result from overdose, misuse or abuse of a medicine.



Pharmacovigilance Terminology con…

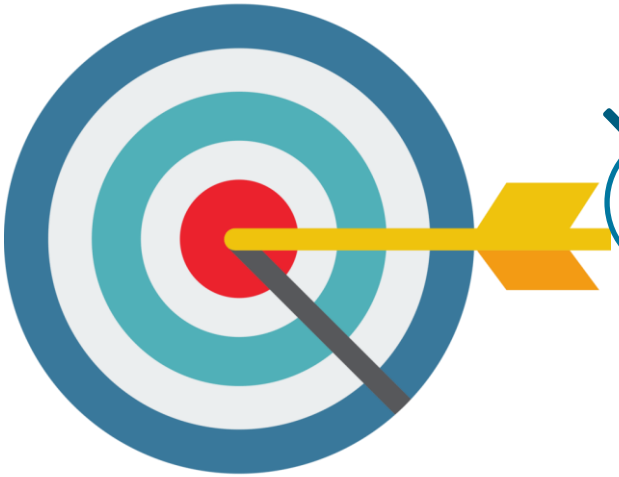
Adverse Effect

A negative or harmful patient outcome that seems to be associated with treatment, including there being no effect at all.

Side Effect

Any unintended outcome (negative or positive effects) that seems to be associated with treatment and can be predicted from the pharmacological profile of the medicine. This term is often used in professional information (PI – previously known as a package insert) and patient information leaflets (PIL) of a medicine. Example: Codeine for cough produces constipation, can be used as a therapeutic effect in traveler diarrhoea.

Objectives of Pharmacovigilance



- Improve safe and rational use of medicines
- Improve patient care, public health and safety
- Improve understanding of benefit-risk profile of medicines
- Detect medicine related problems and communicate the findings in a timely manner
- Promote understanding, education and clinical training in pharmacovigilance

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Types of Pharmacovigilance

Characteristic	Regulatory	Institutional	Public Health Programmes (PHP)
Focal Point	National regulatory authority, pharmaceutical manufacturers	PTC, Academic Researchers, Hospital Quality Assurance Departments, etc.	PHP (in partnership with the regulatory authority and disease surveillance units – e.g., National Pharmacovigilance Center of Programmes (NPC), Expanded Programme for Immunisation (EPI) Maternal, Child and Women's health (MCWH), etc,.
Medicines under focus	All medicines available in the country, particularly newly-marketed/ approved medicines.	Medicines used by health institutions/outreach/satellite facilities or specific patient population/s	Medicines used within the PHP to treat disease under surveillance.
Objectives	Ensure marketed/ approved medicines are safe, effective and of good quality and in public interest.	Minimise institutional drug-related morbidity, mortality and cost	Minimise preventable harm and maintain public trust in the programme and the medicines it employs
Methodologies routinely employed	Spontaneous reporting systems, cohort event monitoring, record linkage studies, etc,.	Case reports and case studies	Targeted spontaneous reporting, cohort studies, case series analysis, rumour surveillance, outbreak/cluster investigation
Communication of results and corrective actions	Regulatory decision-making, market withdrawal, labelling changes, Public Health Advisories, DHCPL, Press Statement.	Newsletters, communication, etc,.	Epidemiological newsletters, press statements, guidelines, training and education materials, local or international publications, infrastructural changes and changes in medicine use

Methods of Pharmacovigilance

Spontaneous Reporting

- Continuous monitoring of all medicines
- All suspected ADRs for all medicines, includes the whole population

Targeted Spontaneous Reporting

- Learn more about the ADR profile of a specific medicines
- Specific ADRs, specific medicines, specific facilities & specific population

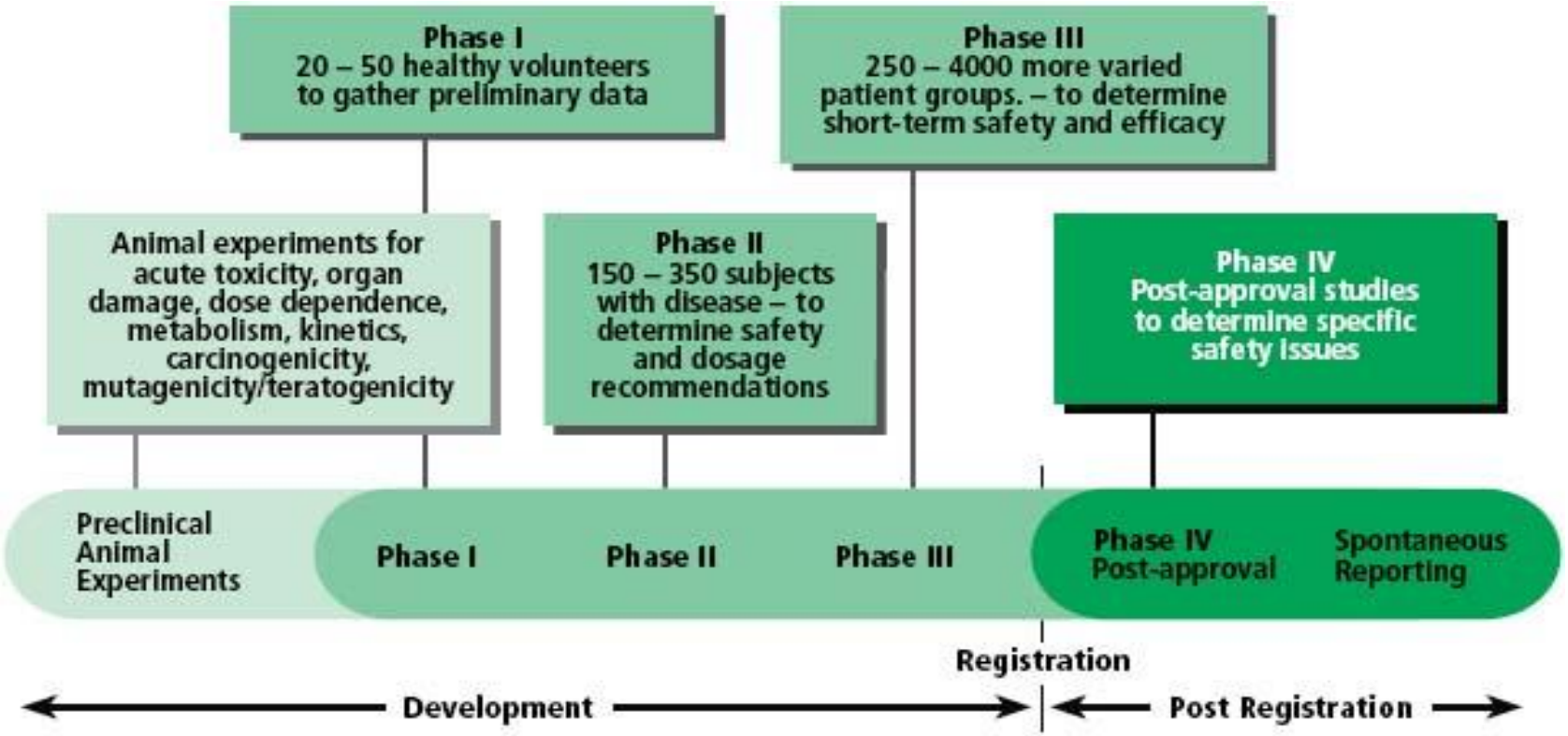
Cohort Event Monitoring

- Systematic collection of all AEs associated with specific medicines e.g. new chemical entity. Quantification of AE rates
- New class of medicine, previous safety issues, potential safety issues

Objective III

Explain why pharmacovigilance is important

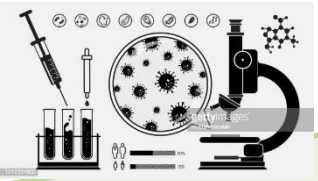
Drug Development Phases



Safety data in Drug Development Phases

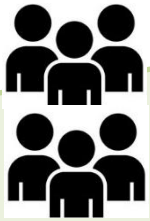
Registration

Pre-Clinical
Lab & animal studies

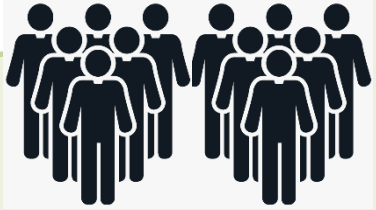


Phase 1
(Tens
Healthy volunteers)

Phase 2
(Hundreds
Subjects with disease)



Phase 3
(Thousands
Wider range of
subjects
with disease)



Phase 4
(Post-marketing)
Entire population
exposed

Major organ & fetal toxicity

Very common ADRs

Common/frequent

Uncommon/Infrequent

Rare/very rare, long term, delayed, Interaction, Misuse/Abuse/ error/product quality effects Pregnancy/birth outcomes

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Limitations of Clinical Trials

Points to consider	Clinical Trials	Clinical Practice
Number of participants	Hundreds to few thousands	Thousands to millions
Duration of exposure	Months	Years
Population	Restricted (Pregnant/children/comorbid)	All
Dose	Fixed	Variable
Conditions	Rigid (e.g., indications are specific)	Flexible (off-label use)

How big is the problem globally?

Review	*n* studies (LMIC)	*n* patients	Proportion of adult medical admissions ADR-related
(1) Einarson, 1993	37 (**2**)	69 187	Median **4.9%** [2.9% to 6.7%]
(2)* Muehlberger, 1997	12 (**0**)	20 037	Median **5.8%** [4.2% to 6.0%]
(3)* Lazarou, 1998	21 (**0**)	28 017	M-A est **4.7%** (3.1% to 6.2%)
(4)* Wiffen, 2001	37 (**3**)	133 741	Weighted mean **3.1%**
(5)* Beijer, 2002	51 (**4**)	116 241	Weighted mean **4.1%**
(6)* Kongkaew, 2008	10 (**1**)	11 477	Median **6.3%** [3.9% to 9.0%]

* in sub-analysis ; [] interquartile range; () 95% confidence interval

How big is the problem of ADRs in South Africa?

Wolters Kluwer **Medicine**

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Medicine (Baltimore). 2016 May; 95(19): e3437. PMCID: PMC4902486
Published online 2016 May 13. doi: 10.1097/MD.0000000000003437 PMID: 27175644

Adverse Drug Reactions Causing Admission to Medical Wards
A Cross-Sectional Survey at 4 Hospitals in South Africa

Hospital Admissions:

- 1 in 12 admissions due to an ADR
- 45% of ADRs were preventable

Mouton JP *et al.* Medicine (Baltimore). 2016 May;95(19):e3437

BJCP British Journal of Clinical Pharmacology — British Pharmacological Society

Br J Clin Pharmacol. 2015 Oct; 80(4): 818–826. PMCID: PMC4594724
Published online 2015 Jul 6. doi: 10.1111/bcp.12567 PMID: 25475751

Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey

Mortality following admission:

- ADRs contributed to the death of 2.9% of medical admissions
- ADR-related deaths of 16%
- 43% of ADRs were preventable

Mouton JP et al. Br J Clin Pharmacol. 2015 Oct;80(4):818-26

How big is the problem of ADRs in South Africa?

[Short title + Author Name - P&H title] 11 (2021) 46–52

Contents lists available at ScienceDirect

African Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/afjem

Original article

Adult medical emergency unit presentations due to adverse drug reactions in a setting of high HIV prevalence

Emergency unit presentations:

- 7.9% were ADR-related. Polypharmacy was an important risk factor

Mouton JP Afr J Emerg Med 2021 11(1):46-52.

Mouton *et al. BMC Pediatrics* (2020) 20:3
https://doi.org/10.1186/s12887-019-1892-x

BMC Pediatrics

RESEARCH ARTICLE Open Access

Serious adverse drug reactions at two children's hospitals in South Africa

Serious ADRs rate:

- 3.8/100
- 23% preventable

Mouton BMC Pediatr 2020, 20(1):3

The Importance of Post-marketing Surveillance

Emerging Fluoroquinolone Safety Concerns

Communications Issued by FDA and EMA

FDA U.S. Food and Drug Administration — Drug Safety Communications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

July 2008 FDA
Tendinitis and tendon rupture; "consider risk/benefit in individuals"

Aug 2013 FDA
Risk of peripheral neuropathy

July 2016 FDA
"Serious side effects associated with FQs generally outweighs the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated UTI" Reserved for those without alternative treatment options. Adverse effects include tendons, muscles, joints, nerves, CNS

May 2018 EMA: Recommendation to restrict the use of fluoroquinolone following a review of disabling and potentially long-lasting side effects

Oct 2018 EMA: New warning regarding risk of aortic aneurysm and dissection associated with fluoroquinolones for systemic and inhalation use

2008 2011 2013 2015 2016 2018

Feb 2011 FDA
Worsening symptoms in patients with myasthenia gravis

Nov 2015 FDA
Advisory Committee meeting

July 2018 FDA: Distinction between warning for mental health and CNS effects; include risk of coma with hypoglycemia

Dec 2018 FDA: "fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body, called the aorta"

Nabriva

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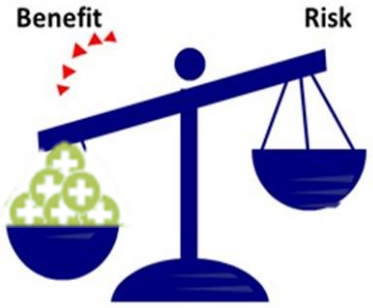
Benefit – Risk Balance

- For a medicinal product to be authorized, the risk/benefit balance should be positive
  - for the target **population**
  - for the approved **indication**



- Therefore, not all risks of harm are identified at the time of marketing

- Continuous safety monitoring is important for all products - to identify and respond to new risks of ADRs.

Any Questions?