Important Definitions in Pharmacovigilance

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definire is to determine the boundaries (Latin fines)

Clarity of communication in the Global village

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Definition: Pharmacovigilance

Pharmacovigilance

- The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

• WHO 2002

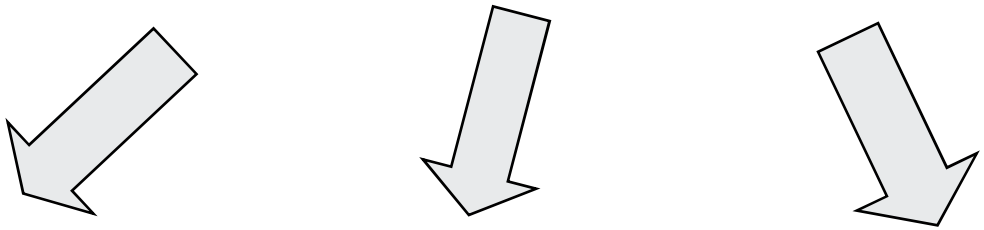
Vaccine Pharmacovigilance

- The science and activities relating to the detection, assessment, understanding and communication of adverse events following immunization and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

• WHO 2012

End Results of Pharmacovigilance Activities

Benefit/risk evaluation



No Change

Monitoring

Edit product information:

Indications/use

Dosing instructions

Contra-indications

Interactions

Pregnancy/lactation

Warnings/precautions

Undesirable effects

Over dosage

Withdraw marketing authorisation

Halt clinical trial

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Definitions: HCP, MAH and ICSR

Health Care Professional (HCP)	medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner, or as otherwise specified by local regulations. ICH E2D
Marketing Authorization	The Company that has the regulatory permission to manufacture and market a product in a given country/Region, and therefore the legal responsibility to comply with pharmacovigilance requirementsHolder (MAH)
Individual Case Safety Reports (ICSR).	Report compiled for each instance of a suspected or confirmed adverse event

Definition: Adverse Event and Adverse Event Following Immunization (AEFI)

Adverse Event

- Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

ICH E2A

An adverse event following immunization (AEFI)

- is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.
- 5 categories of AEFIs :
  - Vaccine product-related reaction
  - Vaccine quality defect-related reaction
  - Immunization error-related reaction
  - Immunization anxiety-related reaction
  - Coincidental event

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Definition: Rate of AE Occurrence

Observed rate

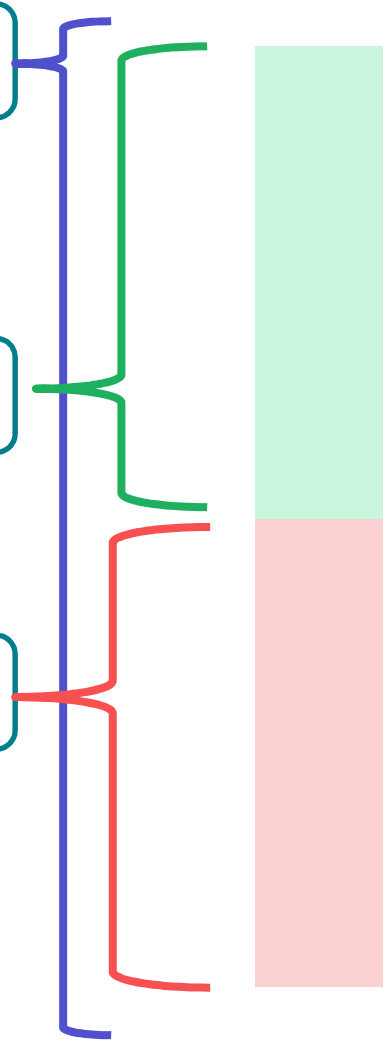
- Total number of cases reported per 1,000 vaccinated children
- Detect in clinical trial or post licensure vaccine safety studies

• Background rate

- Not related to vaccine
- Occur per 1000 unvaccinated children
- Record prior or simultaneously to vaccination

• Vaccine reaction rate

- Related to vaccine
- Detected in placebo controlled randomized clinical trial, or passive surveillance or post licensure studies
- = Observed rate – background rate



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Definition: AEFI Frequency and severity

Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	≥ 10%	**Common and usually minor reactions:** • Are part of the immune response to vaccine, • Reactions settle on their own, • Examples include: ◦ Fever, ◦ Malaise.
Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	**Rare, usually more severe reactions:** 1. Usually require clinical management, 2. Examples include: • Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, • Vaccine specific reactions, such as BCG osteitis.
Rare	≥ 0.01% and < 0.1%	
Very rare	< 0.01%	

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Sources of AE Information

From unsolicited sources

- **Spontaneous Reports**
  - unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organization that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.
- **Literature reports**
- **Internet**
- **Other Sources**
  - e.g. non-medical sources, like the lay press or other media

From solicited sources

- derived from organized data collection systems, which include clinical trials, registries, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.
- Adverse event reports obtained from any of these should not be considered spontaneous.

Definition: Serious Adverse Event (SAE)

An Adverse Event which

- Results in death, OR
- Is life-threatening, OR
- Requires inpatient hospitalization or prolongation of existing hospitalization, OR
- Results in persistent or significant disability/incapacity, OR
- Is a congenital anomaly/birth defect, OR
- Is medically significant

ICH E2A

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Which of the Following is/are Serious?

A 61 year old patient developed seizures and was hospitalized after taking diclofenac tablet orally.

A 12 year old male had a single episode of vomiting after taking paracetamol tablet

A 90 year old female died after developing cardiac arrest. She had consumed one tablet of unknown strength aspirin 2 days back.

A 22 year old male met with a road traffic accident and fractured left forearm. He was taking promethazine orally for the past 4 days.

Severe Event

Severe is used to describe the intensity of a specific event :

- *mild*, *moderate* or *severe*
- the event itself, however, may be of relatively minor medical significance

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Vaccine Reactions

Minor Reactions	Severe Reactions
Usually occur within a few hours of injection	Usually do not result in long-term problems
Resolve after short period of time and pose little danger	Can be disabling
Local (includes pain, swelling or redness at the site of injection)	Are rarely life threatening
Systemic (includes fever, malaise, muscle pain, headache or loss of appetite)	Include seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine

Minor Vaccine Reactions

Vaccine	Local reactions	Systemic reactions	
	(pain, swelling, redness)	Fever > 38°C	Irritability, malaise and systemic symptoms
BCG[a]	90% – 95%	–	–
Hepatitis B	Adults up to 15% Children up to 5%	1 – 6%	–
Hib	5 – 15%	2% – 10%	
Measles/MR/ MMR	~ 10%	5% – 15%	5% (Rash)
OPV	None	Less than 1%	Less than 1%[b]
Pertussis (DTwP)[c]	up to 50%	up to 50%	up to 55%
Pneumococcal conjugate[e]	~ 20%	~ 20%	~ 20%
Tetanus/ DT/aTd	~ 10%[d]	~ 10%	~ 25%
Treatment	• Cold cloth at injection site • Paracetamol[f]	• Give extra oral fluids • Wear cool clothing • Tepid sponge or bath • Paracetamol[f]	• Give extra oral fluids

Severe Vaccine Reactions

Severe vaccine reactions, onset interval, and rates associated with selected childhood vaccines

Vaccine	Reaction[a]	Onset interval[26]	Frequency per doses given
BCG[28]	Fatal dissemination of BCG infection	1 – 12 months	0.19 – 1.56/1,000,000
OPV[29]	Vaccine associated paralytic poliomyelitis (VAPP)[b]	4 – 30 days	2 – 4/1,000,000
DTwP[30]	Prolonged crying and seizures[c]	0 – 24 hours	< 1/100
	HHE	0 – 24 hours	< 1/1,000 – 2/1,000
Measles[31]	Febrile seizures	6 – 12 days	1/3,000
	Thrombocytopenia	15 – 35 days	1/30,000
	Anaphylaxis	1 hour	1/100,000

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Definition: Minimum Criteria for Reporting

An identifiable patient

- Age (or age category, e.g., adolescent, adult, elderly)
- gender
- initials
- patient hospital number

A suspect medicinal product

An identifiable reporting source

- e.g. name, contact information and address of Reporter

At least one adverse event

Minimum Criteria for Reporting - Example

Mini net

Reporting source

Suspected drug

Adverse Event

Identifiable patient

- A pharmac pharmacy rep ted that a 12 year old male eveloped acute allergic reaction after taking amoxicillin 250 mg orally

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Minimum Criteria for Reporting - Example

Minimum criteria NOT met

Suspected drug missing

- A pharmacist from XYZ pharmacy reported th[illegible] a 12 year old male developed acute allergic reacti[illegible]n after taking unknown drug orally

Definition: Expectedness – of an Adverse Event

Unexpected AE/SAE

- An adverse event, the nature, severity, specificity or outcome of which is not consistent with the applicable product information*
- *Unapproved investigational product - Investigator's Brochure
- Approved product - Prescribing Information /Pack Insert/ Summary of Product Characteristics

Definition: Relatedness – of an Adverse Event

AE/SAE may be related or unrelated to the drug

Done by Causality assessment, which is defined as:

- The evaluation of the likelihood that a medicine is the causative agent of an observed adverse event

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Methods of Causality Assessment

Key parameters for doing causality assessment:

- Pharmacodynamic effects of the drug
- Temporal relationship (timing of dose)
- De-challenge, re-challenge information
- Class effects of the drug
- Previous reports (e.g. literature reports)
- Concomitant medications
- Concomitant illness

Methods

- No standard method recommended by any of the Regulatory Authorities.
  - Probability calculation (Bayes' Theorem)
  - French imputation systems
  - The Naranjo ADR Probability Scale
  - The European ABO Systems
  - The US Reasonable Possibility Systems
  - Global introspection method – **WHO- UMC causality assessment scale** is one of the most widely used

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Signal Detection

The WHO defines a signal as reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously

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Signal Detection

Rule of "Three"

There is 95% chance of observing one occurrence of an event in a population 3 times the size of the event's frequency

- e.g. if the incidence is 1 / 10,000
- 30,000 patients need to be studied to find ONE case

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Signal Detection – Importance of Data Collection

Expected incidence of ADR/AEFI	Required number of ADR/AEFI		
	1	2	3
1 in 100	300	480	650
1 in 200	600	900	1300
1 in 1000	3000	4800	6500
1 in 2000	6000	9600	13000
1 in 10000	30000	48000	65000

Evans, S. J. W. (2005) Statistics: Analysis and Presentation of Safety Data, in Stephens' Detection of New Adverse Drug Reactions, Fifth Edition (eds J. Talbot and P. Waller), John Wiley & Sons, Ltd, Chichester, UK.

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