Vaccine safety surveillance

Vaccine Pharmacovigilance

Definition- According to the CIOMS/WHO working group on vaccine pharmacovigilance, Vaccine pharmacovigilance is defined as "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 effect of the vaccine or immunization.

Importance of vaccine safety

- Decreases in disease risk and increased attention on vaccine risks
- Public confidence in vaccine safety is critical
- Low tolerance for vaccine risks
  - Higher standard of safety is expected
  - Vaccinees generally healthy
  - Lower risk tolerance = need to search for rare reaction

Steps of vaccine pharmacovigilance

Detect signal suggesting AEFI is related to vaccine.

Develop hypothesis about causal association between an AEFI and vaccination

Test hypothesis through appropriate epidemiological method

Vaccine provide by Govt. of India

Govt. of India is providing vaccination to prevent 7-vaccine preventable disease (VPDs) namely,

- ✓ Diphtheria,
- ✓ Pertussis,
- ✓ Tetanus,
- ✓ Polio,
- ✓ Measles,

- ✓ Hepatitis B,
- ✓ BCG
- ✓ JE vaccination,
- ✓ Hib (given as pentavalent containing Hib+DPT+Hep B)

Other vaccines.....

- ➢ Pneumococcal vaccine
- ➢ Rotavirus vaccine
- ➢ Hepatitis A
- ➢ MMR
- ➢ Influenza
- ➢ Meningococcal
- ➢ Cholera
- ➢ JE
- ➢ HPV
- ➢ Varicella
- ➢ Typhoid

Source for vaccine safety

- Local health workers
- Health education campaigns
- Visiting experts
- Online resources and communication network
- Religious and/or community leader
- Parents, guardians and vaccine
- Radio and telivision
- printed material
- Video or DVD

Which AEFIs should be reported?

- Serious AEFI

- Signal and events associated with newly introduced vaccine
- AEFI that may have been caused by an immunization error
- Significant events of unexplained cause occurring within 30 days after a vaccination
- Event causing significant parental or community concern
- Swelling, redness, soreness at the injection site IF it lasts for more than 3 days or swelling extended beyond nearest joint

Adverse event following immunization (AEFI)

Definition-

An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptoms or disease.

Classification of AEFIs

- **Vaccine product-related reaction** – An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. Extensive limb **e**.g. swelling following DTP vaccination.
- **Vaccine quality defect-related reaction** – An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product inducing its administration device as provide by the manufacturer.

Ex. Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

- **Immunization error-related reaction** – An AEFI that is caused by inappropriate vaccine handling, prescribing or administration.

Ex. Transmission of infection by contaminated multidose vial.

- **Immunization anxiety-related reaction** – An AEFI from anxiety about the immunization.

  e.g. Vasovagal syncope in an adolescent following vaccination.
- **Coincidental event**- An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

  e.g. A fever after vaccination (temporal association) and malarial parasite isolated from blood

AEFI Frequency Terminology

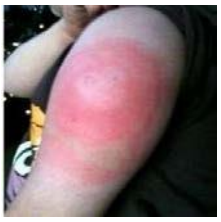
Very common*	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1,000 and < 1/100	≥ 0.1% and < 1 %
Rare	≥ 1/10,000 and < 1/1,000	≥ 0.01% and < 0.1%
Very rare*	< 1/10,000	< 0.01%

Two type of vaccine reaction-

- Minor reaction
- Severe reaction

Minor reaction

- Usually occur within a few hours of injection.
- Resolve after short period of time and pose little danger.
- Local (includes pain, swelling or redness at the site of injection).
- Systemic (includes fever, malaise, muscle pain, headache or loss of appetite).



Severe reaction

- Usually do not result in long-term problems.
- Can be disabling.

- Are rarely lives threatening?
- Include seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine.

Serious AEFI cases (formats and timelines)

Type of Report		Responsible	Time line
CASE REPORTING FORM(CRF)		MO	24 hours of notification
		DIO	48 hours of notification
CASE INVESTIGATION FORM (CIF)	Preliminary	DIO	10 days of notification
	Final	AEFI investigation team	70 days of notification

Vaccine Evaluation

Pre-licensing

Randomised, Blinded, Controlled Clinical Trials

Vaccine efficacy:

Protective Effect under Idealised Conditions

RTC: controlled experiments, simple interpretation

Post-licensing

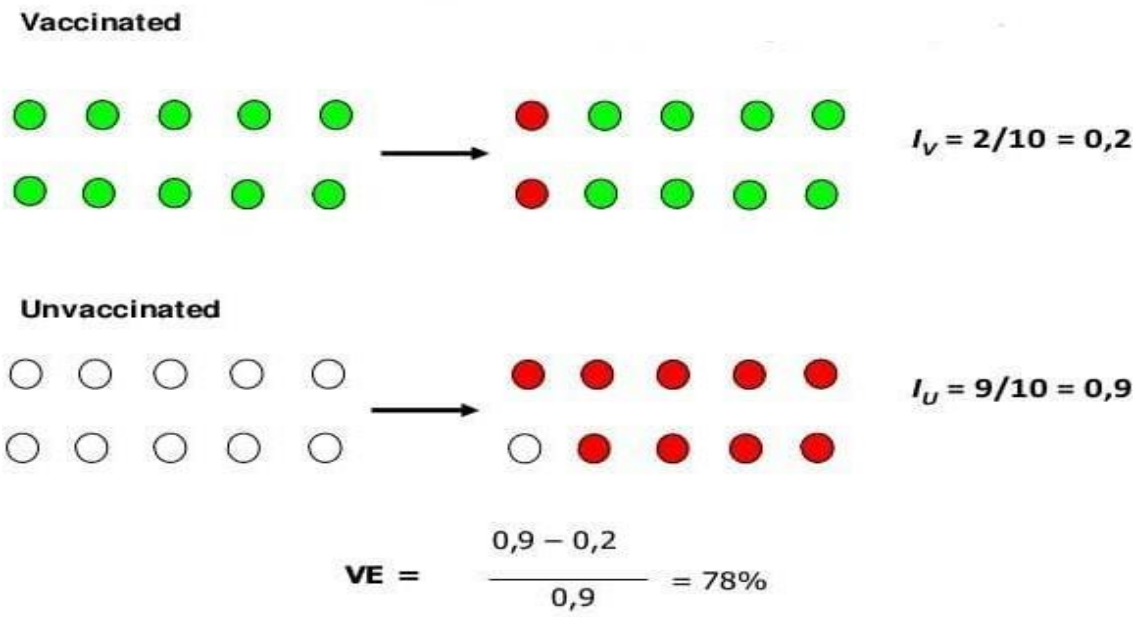
Observational Studies

Vaccine effectiveness

Protective Effect under Ordinary Conditions of a public health programme

Prone to bias, more complex interpretation

Basic Calculation of Vaccine Evaluation



VE(%) = (ARU-ARV/ARU).100

Precaution-

- A condition in a recipient which may increase the chance or severity of an adverse event, or
- May compromise the ability of the vaccine to produce immunity.

Pharmacovigilance Methods

Objective

- ✓ To establish a functional reporting system to monitor the safety of all medicines
- ✓ To learn more about the safety profile of new medicines in the early post-marketing phase
- ✓ To learn more about the ADR profile of a specific medicine(s) in your population
- ✓ To estimate the incidence of a known ADR to a specific medicine in your population
- ✓ To gather more information on the safety profile of a new chemical entity in early post-marketing phase

- ✓ To make use of existing electronic health records and registries to support pharmacovigilance activities

Methods-

- Passive surveillance
  - Spontaneous reports
  - Case series
- Stimulated reporting
- Active surveillance
  - Sentinel sites
  - Drug event monitoring
  - Registries
- Targeted clinical investigations
- Comparative observational studies
  - Cross sectional study
  - Case control study
  - Cohort study
- Descriptive studies
  - Natural history of disease, Drug utilization study

Spontaneous Reports

- ➢ A communication by consumers or healthcare professionals to a company or Regulatory Authority, that describes one or more ADR in a patient, who has given the drug.
- ➢ It plays a major role in the, identification of safety signals once the drug is marketed.
- ➢ Gives alerts on rare AEs that were not detected in earlier clinical trials or pre marketing studies.
- ➢ Provides important information on at risk groups, risk factors and clinical features of known serious ADRs.

Case series

- Series of case reports can provide evidence of an association of a drug and AEs.
- Generally more useful for generating hypothesis than for verifying an association between drug exposure and outcome.
- Certain distinct adverse events occur more frequently with drug therapy, such as anaphylaxis, aplastic anemia and Stevens-Johnson syndrome events such as these are spontaneously reported for detailed and rapid follow-up.

Stimulated Reporting

- A method used to encourage and facilitate reporting by health professionals for new products, or for limited period.
- Online reporting of AE, systematic stimulation of reporting of AEs.
- Drawbacks- data are often incomplete.

  Not useful to generate accurate incidence rates.

Active surveillance

- To ascertain completely the no. of AEs via a continuous pre-organized process. E.g. follow up of patient treated with a particular drug.
- More feasible to get comprehensive data on individual AE reports.

Sentinel Sites:- Active surveillance carried out at Institutions, Nursing Homes and Hospitals etc. provides information such as data from specific patient subgroups, drug abuse etc.

Drug Event Monitoring: - Patients are identified by electronic prescription data or automated health insurance claims. A follow up questionnaire can be sent to each physician or patient at specified intervals. Information on patient demographics, indication for treatment, duration of therapy, dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Registries: - A registry is a list of patients presenting with same characteristics. E.g. Disease registry, drug registry, pregnancy registry etc. Differs from each other depending on type of patient.

Comparative Observational Studies:-

- Traditional epidemiologic methods are a key component in the evaluation of AEs.
- Observational study designs are useful in validating signals from spontaneous reports or case series.

Cross Sectional Studies:-

- Data collected from a population of patients at a single point in time regardless of exposure or disease status.
- Primarily used to gather data for surveys or for ecological analysis. Best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured.

Case Control Study:- In this case of disease are identified. Controls or patients without the disease or event of interest, are selected from the source population. Exposure status of the two groups is compared using the odds ratio.

Cohort Study:- A population at risk for the disease is followed over a time for the occurrence of the disease or events. Information on exposure status is known throughout the follow up and hence incident rates can be calculated.

Comparison cohorts of interest are selected on the basis of drug use and followed over time. Multiple AEs can also be investigated using the same data source in a cohort study.

Targeted Clinical Investigations:-

- When significant risks are identified from pre-approval clinical trials, further clinical studies might be called, to evaluate the mechanism of action for ADRs.
- PK and PD studies might be conducted.
- Specific studies to investigate potential drug-drug interactions and food-drug interactions might be called.

Descriptive Studies:-

- Primarily used to obtain the background rate of outcome events and/or to establish the prevalence of the use of drugs in specified populations.

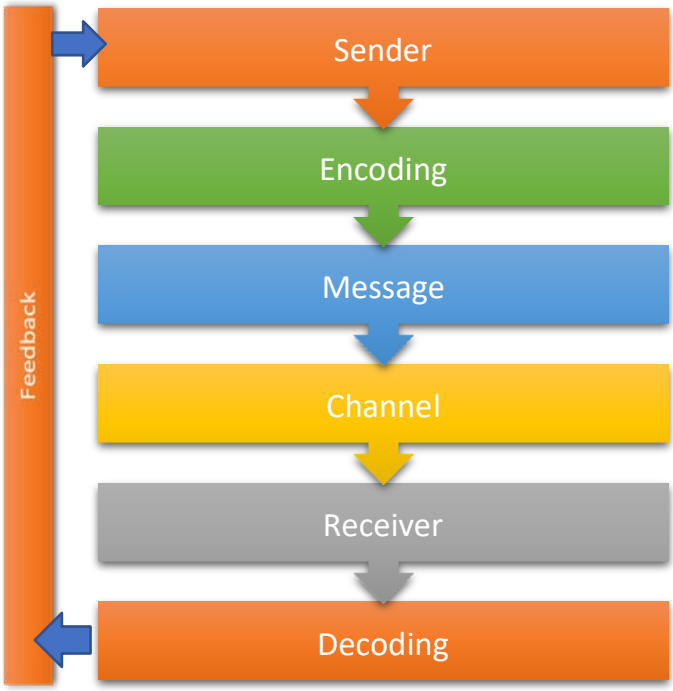
- Natural History of Disease- Focused on the natural history of disease, including the characteristics of diseased patient and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest.

Drug Utilization Study- These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

Communication:

The act of sharing or exchanging information, ideas or feelings.

- Communication Process:



- **Principles of Good Pharmacovigilance Communication**
  - ✓ Relate the messages to the audience's perspective
  - ✓ Avoid comparisons which trivialize the concern
  - ✓ Ensure completeness of the message
  - ✓ Be balanced, honest and sympathetic
  - ✓ Focus on the specific issue that needs to be handled

- ✓ Pay attention to what the audience already knows
- ✓ Be respectful of people's right to be concerned
- ✓ Be honest about the limits to scientific knowledge
- ✓ Acknowledge uncertainty
- ✓ Evaluate the impact of your message

- Effective Communication in Pharmacovigilance

One can achieve effective way of communication just by following the principles of good pharmacovigilance communication.

- **Why do we need to improve our communication?**
  - ✓ Improve patient care and understanding
  - ✓ Eradicate disease / improve disease control
  - ✓ Promote transparency and accountability
- **Why do Communications matter in Drug Safety?**
  - ✓ For Welfare of millions of people worldwide
  - ✓ To overcome Extreme dangers of failure
  - ✓ Communications are commonly poorly executed, second-rate and ineffective, so to improve the quality.
- **Communication Challenges:**
  - ✓ The importance of ADRs and reporting them
  - ✓ Information about benefit – harm and effectiveness – risk
  - ✓ Encouraging rational drug use/adherence
  - ✓ Communicating uncertainty
  - ✓ Dealing with traditional beliefs and practices
  - ✓ Involving patients; reaching informed consent
  - ✓ Preventing or resolving crises

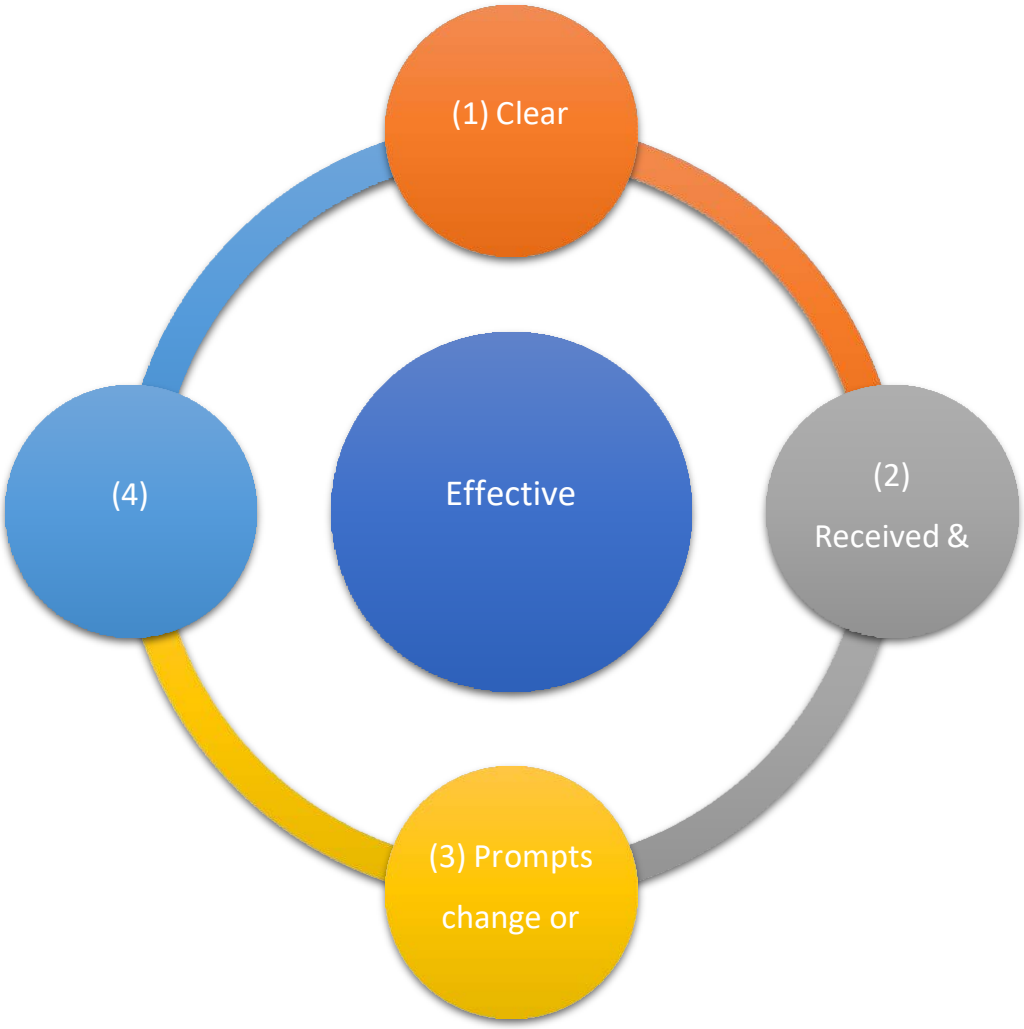
Problematic issue in Drug Safety:

all reliant on communications for safety

- ✓ Adverse effects: 'no drug 100% safe'
- ✓ Risk as a concept in medicine

- ✓ Safety and medicines (prescribing, dispensing)
- ✓ Benefit-harm
- ✓ Effectiveness-risk
- ✓ Public health and commercial goals
- ✓ Public health and individual welfare
- ✓ Access to medicines
- ✓ Uncertainty

What is an Effective Communication?



Principles of Effective Communications

- ✓ Be clear about your message and purpose
- ✓ Know your audience(s): empathy; tailor the message
- ✓ Choose appropriate methods/media
- ✓ Present message with impact
- ✓ Make benefits clear
- ✓ Pre-test and revise message
- ✓ Repeat message
- ✓ Seek feedback, monitor effects, start again

Qualities of Modern Communications:

- ✓ Intimacy
- ✓ Immediacy and high impact
- ✓ Peer-to-peer
- ✓ Addressing competition and low attention levels
- ✓ Benefits

Planning Communications:

- ✓ Today's modern standards and methods
- ✓ Simple, clear message
- ✓ Stimulating motivation and offering benefits (including rewards and feedback)
- ✓ The use of specialist skills and creative imagination

Summary:

- Our communications must:

– Be strong and visible

– Be precisely targeted and tested

– Change attitudes, values, behaviour

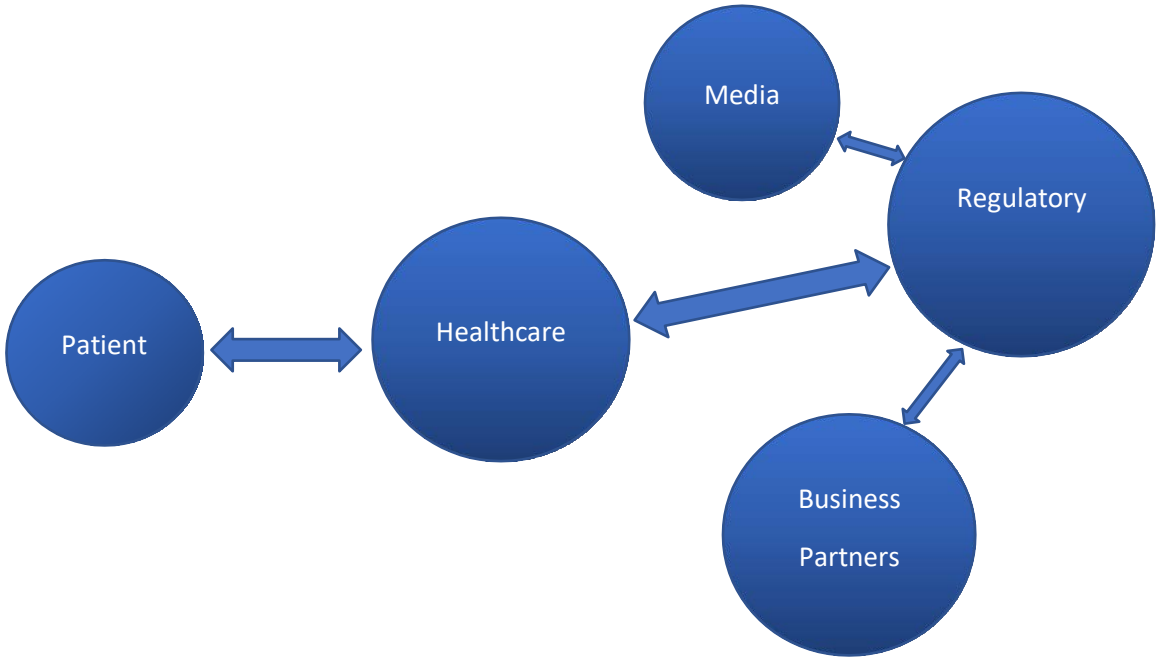
– Be followed up and revised

– Embrace modern standards and skills

1. Communication in Drug Safety Crisis Management

- Crisis will happen (fire, death, ADRs…)
- Assess risks
- Anticipate and plan for all likely and unlikely events
- Create, rehearse and revise crisis plans
- In crisis, communicate
  - – Quickly
  - – Openly and honestly
  - – Express regret, apologise
  - – Explain what is being done to solve the crisis and prevent repetition

2. Communicating with Regulatory Agencies, Business partners, Healthcare facilities & Media



Communication with Media:

- **Who are the media?**
  - ✓ Print -magazines, newspapers, community newspapers
  - ✓ Electronic -radio, TV, internet
  - ✓ Local and national levels

- **Partners & Audiences in Drug Safety:**

Partners

- Manufacturers
- Regulators
- Politicians
- Employees
- Health professionals
- Academics
- Bosses/managers

Audiences

- The public
- Patients
- Consumer groups
- Lawyers
- The media
- International community