IIHMR UNIVERSITY

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Faculty Development Program for IIHMR Group of Institutions

Immunization Safety Surveillance & Vaccine Pharmacovigilance

Date: December 19, 2020

Dr. Krishna Kumar S
Associate Professor
IIHMR Bangalore

Over 3 years of overseas work experience in Singapore Health System in the field of hospital epidemiology and disease surveillance, providing of public health intelligence and hospital epidemiology services and expert advice in the prevention, control and containment of communicable disease outbreaks emerging infectious diseases and nosocomial infections. Provide information for strategic planning and decision making by senior management and policy makers in these areas of public health specialization and hospital healthcare improvement and participate and represent in the intra-hospital programmes, inter-hospital committees or MOH committees.

Over 4 years work experience in Indian health systems in the field of Reproductive, Maternal, Newborn, Child Health (RMNCH+A)Programs with strategic approach to provide an understanding of 'continuum of care' to ensure equal focus on various life stages to track health outcomes to address the major causes of mortality among women and children in the High Priority Districts of Kerala, Tamil Nadu, Puducherry State, India. Also Developed dashboard for End Adolescent HIV/AIDS – ALL IN phase 1 rapid assessment for India country level.

Over 3 years work experience at sub national level on immunization safety surveillance and vaccine pharmaco-vigilance for improving patient safety, vaccine safety reports, Surveillance & Epidemiology of Vaccine ADRs, data analysis, policy inputs, implementing online reporting of Surveillance and Action For Events following Vaccination – SAFE-VAC.

Immunization Safety Surveillance & Vaccine Pharmaco-vigilance

19th December 2020.

Faculty Development Program, IIHMR-Bengaluru, Karnataka.

Dr. S. Krishna Kumar,

Associate Professor- Medical Epidemiologist

IIHMR, Bangalore

Learning outcomes

- **Know the definition of Vaccine Pharmacovigilance, AEFI.**
- **Know the importance of immunization safety surveillance system in India.**
- **Appreciate the need for specialized monitoring of vaccine ADRs /AEFI especially the public health imperatives.**
- **Safety profile of new vaccine introduction- covid 19 vaccine, dengue vaccines.**

Section 1

INTRODUCTION TO VACCINE PHARMACOVIGILANCE

Purpose of Vaccine ADR / AEFI surveillance

- Immunization is one of the most effective public health interventions for protecting the individual & the public from vaccine-preventable diseases.
- Immunization has saved millions of lives. Modern vaccines are safe and effective. However, like other medicinal products, vaccines are not completely free from adverse events/ reactions.

Vaccine ADR / AEFI Surveillance

- Vaccine pharmacovigilance, which includes the surveillance of AEFI/ ADR should be part of all immunization programmes as this helps sustain public confidence in the programme.
- Vaccines used in national immunization programmes are extremely safe and effective. Nevertheless, no vaccine is perfectly safe and adverse events may occur.
- In addition to the vaccines themselves, the **process of immunization** is a potential source of an adverse event /reaction.

Case Study Report 1

- In 1955, after administration of inactivated polio vaccine manufactured by Cutter Laboratories in the USA, 40 000 people developed abortive polio, 200 were permanently paralysed and 10 died. Investigations revealed that two production pools of 12 000 doses contained live virus.
- **Cause: Vaccine quality defect-related reaction**
- See:http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/.

Case Study Report 2

In 1992, in a hospital in country A, five neonates collapsed a few minutes after immunization with BCG. Four were resuscitated and one died. Muscle-relaxant drugs were found in the refrigerator in which the vaccines were kept.

Cause: Immunization error-related reaction. Use of muscle-relaxant instead of diluent.

In 1997, in country C, 21 infants died out of 70 infants supposedly given DTP vaccine. Insulin was stored in similar vials and in the same refrigerator as the DTP vaccine.

Cause: Immunization error-related reaction. Use of insulin instead of DTP.

Case Study Report 3

- Anaphylaxis is a known reaction to rubella vaccine. (Rubella vaccine used in this country has contained gelatine, and the link between gelatine and red meat, leading to severe allergic reactions, is documented in medical literature). Inj. Adrenaline is the drug of choice for anaphylaxis management.
- South Indian state, Particular district with majority vegetarian population : Rubella vaccine.

- **Cause : Vaccine product-related reaction.**

Case Study Report 4

- Case study In 2004, a school-based mass measles-rubella immunization campaign was conducted among young adolescents aged 12–19 years in country D.
- On the first day, 44 children were hospitalized with hyperventilation and / or vomiting. An investigation concluded that more than 90% of the cases were anxiety reactions and all but two cases were discharged from hospital the same day.
- **Cause: Immunization anxiety-related reactions/ Immunization Triggered Stress Response.**

Case Study Report 5

In 2010, six infants died within 48 hours following administration of pentavalent (DTP-HepB-Hib) vaccine in country F. Use of the vaccine was temporarily suspended. A high-level investigation was carried out as the deaths had led to public concern and health staff were reluctant to use the vaccine.

Investigation and assessment revealed that, out of six cases, three were confirmed as coincidental event (1-suffocation and 2- sepsis due to underlying infections). Of the other three cases, one was diagnosed as anaphylaxis and the other two were inconclusive.

Cause: 3 Coincidental & 1 Vaccine product related reaction, 2 inconclusive.

SIDS/ SUDI following Immunization

- **Do we need to report Sudden Infant Death Syndrome (SIDS) and Sudden Unexplained Death of Infant (SUDI) after immunization through ADR/ AEFI Surveillance ?**
  - **YES/ NO/ MAY BE/ NOT CLEAR / WHY**
- **Infant Death Review committee do they review past medical history of immunization?**
  - **YES/ NO/ MAY BE/ NOT CLEAR / WHY**

- http://sids.org/category/news/
- http://www.ncbi.nlm.nih.gov/pubmed/22289512
- http://www.ncbi.nlm.nih.gov/pubmed/24083600

Definition of Vaccine Pv

- Vaccine pharmacovigilance is defined as the science and activities relating to the **detection**, **assessment**, **understanding**, **prevention**, and ***communication*** *of adverse events following immunization, or of any other vaccine-or immunization-related issues*
- *–Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.*

Why Vaccine Pharmacovigilance?..1

1. **Vaccines are usually administered to healthy people, including infants**

2. **Vaccines may be administered to the vast majority of the population or of a large birth cohort or to groups at high risk for diseases.**

3. **Subpopulations may be more susceptible to experience certain AEFIs.**

4. **The age at the time of immunization may coincide with the emergence of certain age-related diseases (e.g. SIDS, neurodevelopmental disorders)**

5. **Immunization with certain vaccines is mandated in some countries.**

6. **The benefits of immunization may not be immediately visible, particularly if the target disease incidence is low. Vaccines may elicit herd immunity also.**

Why Vaccine Pharmacovigilance?...3

- 7.Vaccines are often administered concomitantly with other vaccines, other drugs making causal attribution to a specific vaccine is difficult.

- 8.The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccinees or their contacts and should be differentiated from coinciding natural infection.

- 9.Therefore AEFIs should be recognized by HCPs and reported through health system and also to be monitored.

Why adverse drug reactions to be recognized and reported by health care professionals?

- **To Ensure Patient Safety**

- **To monitor Drug / Vaccine Safety**

Differences between Vaccines & Other Drugs

Vaccines

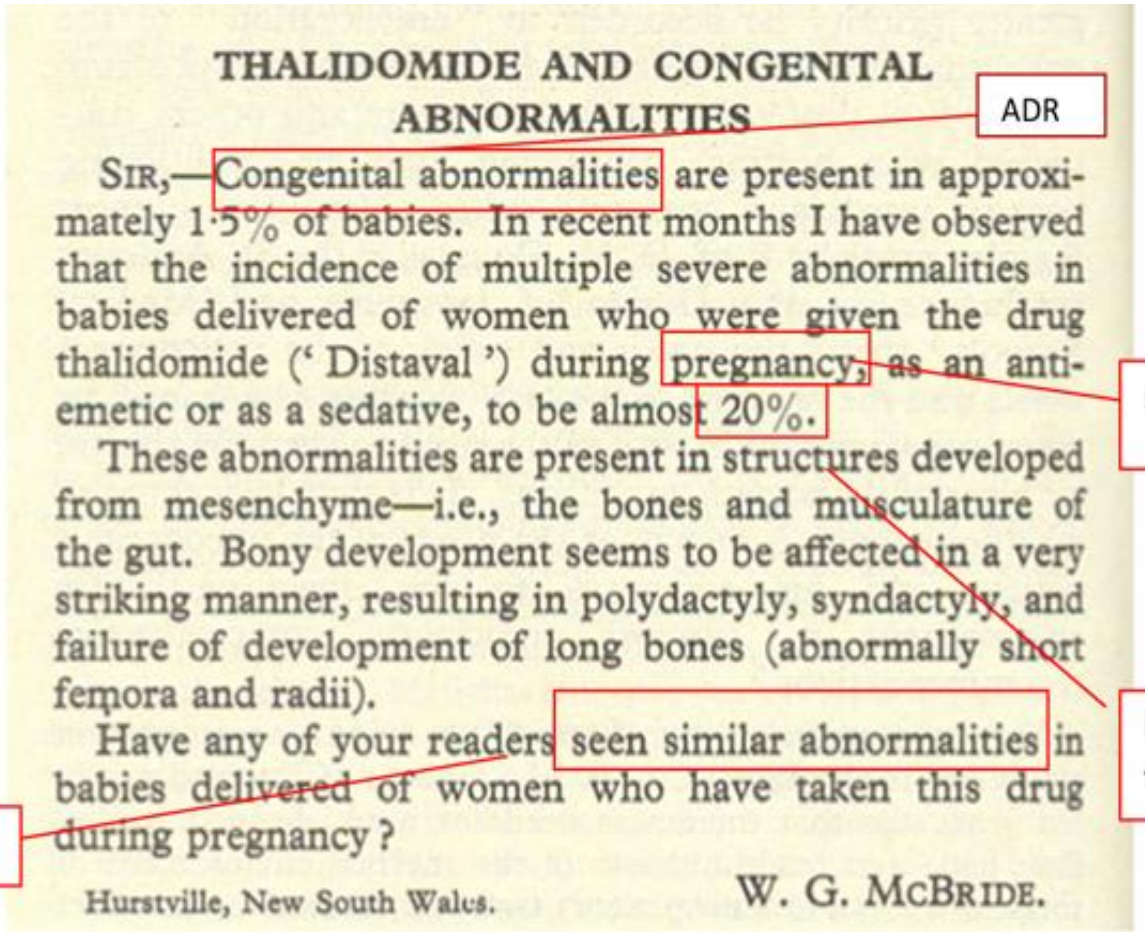
1. Prevention in healthy, larger population
2. Lower risk tolerance
3. Limited number of products single dose.
4. Greater potential for temporal “coincidence”
5. Prone to “program error”
6. Cold chain often critical
7. Biological product – more prone to lot variation and instability
8. Mass campaigns: many doses in short time, defined population
9. Issues of coordination public health system /NIP, NRA and manufacturers

Other Drugs

1. Treatment in ill, sick patients, smaller population
2. More tolerant of risk
3. Large number of products, many classes of drugs.
4. Treatment over time: less “coincidence" after a single dose
5. Less prone to administration error
6. Cold Storage/handling less critical
7. Chemical product – more stable or less prone to instability.
8. No mass campaigns – “private” prescribing to less defined population
9. Less Issues of coordination between health system / Govt/NRA and manufacturers.

Origin of ADR Reporting

Dr William McBride, Australia



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.

ADR

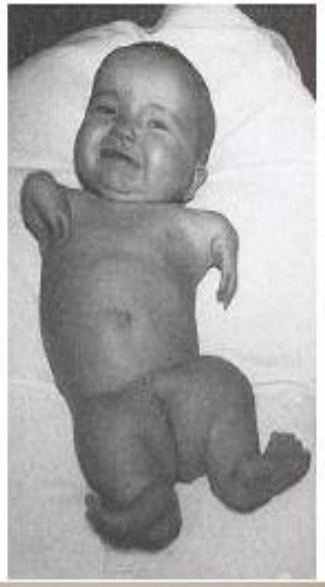
Risk group

Increased frequency

Confluence of data

Origin of Drugs Safety Vigilance

- Thalidomide tragedy 1957 -1961



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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 oversess 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.—ED.L.

Dr William McBride, Australia

Link between MMR vaccine and autism

- The Lancet paper, authored by **Andrew Wakefield** and eleven co-authors, claimed to link the MMR vaccine to autism and colitis, spectrum disorders.
- The Lancet paper was partially retracted in 2004 and fully retracted in 2010, when Lancet's editor-in-chief described it as **"utterly false."**
- Wakefield was found guilty by the General Medical Council of serious professional misconduct in May 2010 and his name was erased from General Medical Register-UK, meaning he could no longer practise as a doctor in the UK. original paper as fraudulent.
- All the autism case details were given by one lawyer.


THE LANCET

CORRESPONDENCE | VOLUME 354, ISSUE 9182, P949-950, SEPTEMBER 11, 1999

MMR vaccination and autism

Andrew J Wakefield

Published: September 11, 1999 • DOI: https://doi.org/10.1016/S0140-6736(05)75696-8

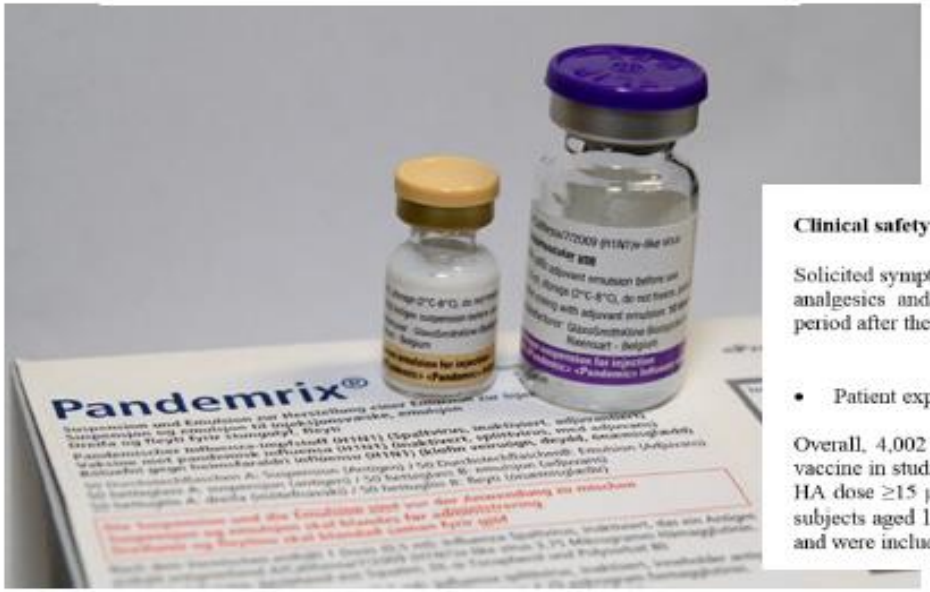
Sir

The Flu Vaccine : Pandemrix

European Medicines Agency
Evaluation of Medicines for Human Use

CHMP ASSESSMENT REPORT
FOR
Pandemrix

Common Name:
Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)



Each 0.5 ml dose of vaccine has the following composition:

Active Ingredient:	
Purified antigen fractions of inactivated split virion A/Vietnam/1194/2004 NIBRG-14 (H5N1)	3.75 µg HA
Adjuvant:	
Squalene	10.68 mg
Alpha-tocopherol	11.86 mg
Polysorbate 80	4.86 mg

Other Ingredients:
Octoxynol 10
Sodium chloride
Disodium phosphate
Potassium dihydrogen phosphate
Potassium chloride
Magnesium chloride
Thiomersal
Water for injections

Clinical safety

Solicited symptoms were recorded during the 7-day follow-up period after each dose together with any analgesics and/or antipyretics taken. Unsolicited symptoms occurring during a 21-day follow-up period after the first vaccination and 30 days after the second one were also recorded in the CRF.

- Patient exposure

Overall, 4,002 healthy subjects (minimum age 18 years) were exposed to H5N1 AS03 adjuvanted vaccine in studies 007 and 008 i.e. total across all doses. More than 3800 of these subjects received an HA dose ≥15 µg i.e. at least 4-fold the HA dose in the intended marketed formulation. Another 961 subjects aged 18-60 years received at least one dose of Third series 3.8 µg/AS03 vaccine in study 002 and were included in the safety evaluation.

Pandemrix-Narcolepsy–July 2011

The AEFI - narcolepsy

REVIEW ARTICLE

Narcolepsy

Thomas E. Scammell, M.D.

N Engl J Med 2015; 373:2654-2662 | December 31, 2015 | DOI: 10.1056/NEJMra1500587

nature genetics

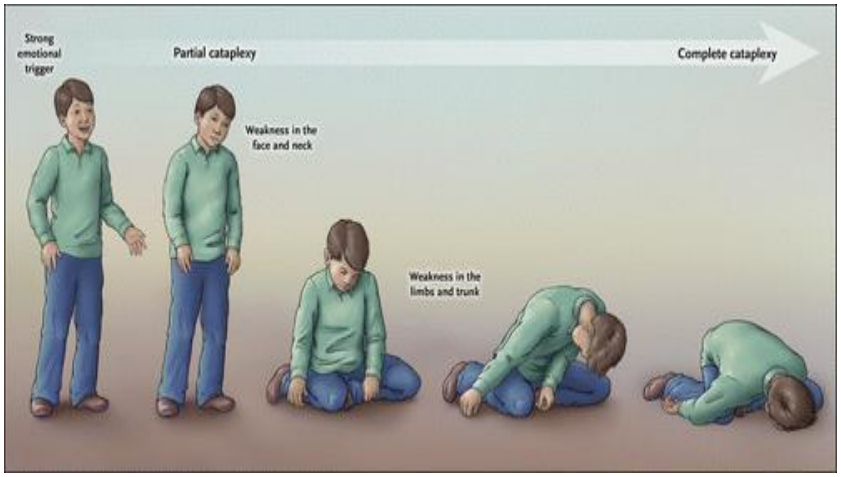
News & Views | Published: 01 June 2009

Narcolepsy and the T-cell receptor

Timothy J Vaughan

Nature Genetics 41, 640–641 (2009) | Download Citation

The etiology of the sleep disorder narcolepsy has not been firmly established, although an autoimmune pathogenesis has been proposed and is supported by a strong genetic association with the HLA. A new genome-wide association study provides further support for the autoimmune basis of narcolepsy by uncovering a robust association at the T-cell receptor alpha locus.



EUROPEAN MEDICINES AGENCY
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Medicines ▾ Human regulatory ▾ Veterinary regulatory ▾ Committees ▾ News & events ▾ Partners & networks ▾ About

European Medicines Agency recommends restricting use of Pandemrix

Share

Press release 21/07/2011

In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.

Finalising its review of Pandemrix and narcolepsy the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunisation against H1N1 is still needed (e.g. in persons at risk of the complications of infection). The CHMP confirmed that overall the benefit-risk balance of Pandemrix remains positive.

The Committee noted that the vaccine is likely to have interacted with genetic or environmental factors which might raise the risk of narcolepsy, and that other factors may have contributed to the results. There are several initiatives being developed across the EU to further investigate this association.

Pandemrix-Narcolepsy–July 2011

How did it happen?

RESEARCH ARTICLE | NARCOLEPSY

CD4+ T Cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy

Alberto K. De la Herrán-Arita[1,*], Birgitte Rahbek Kornum[1,2,*], Josh Mahlios[1], Wei Jiang[3], Ling Lin[1], Tieying Hou[3], Claudia Mac...
+ See all authors and affiliations

Science Translational Medicine 18 Dec 2013:
Vol. 5, Issue 216, pp. 216ra176
DOI: 10.1126/scitranslmed.3007762

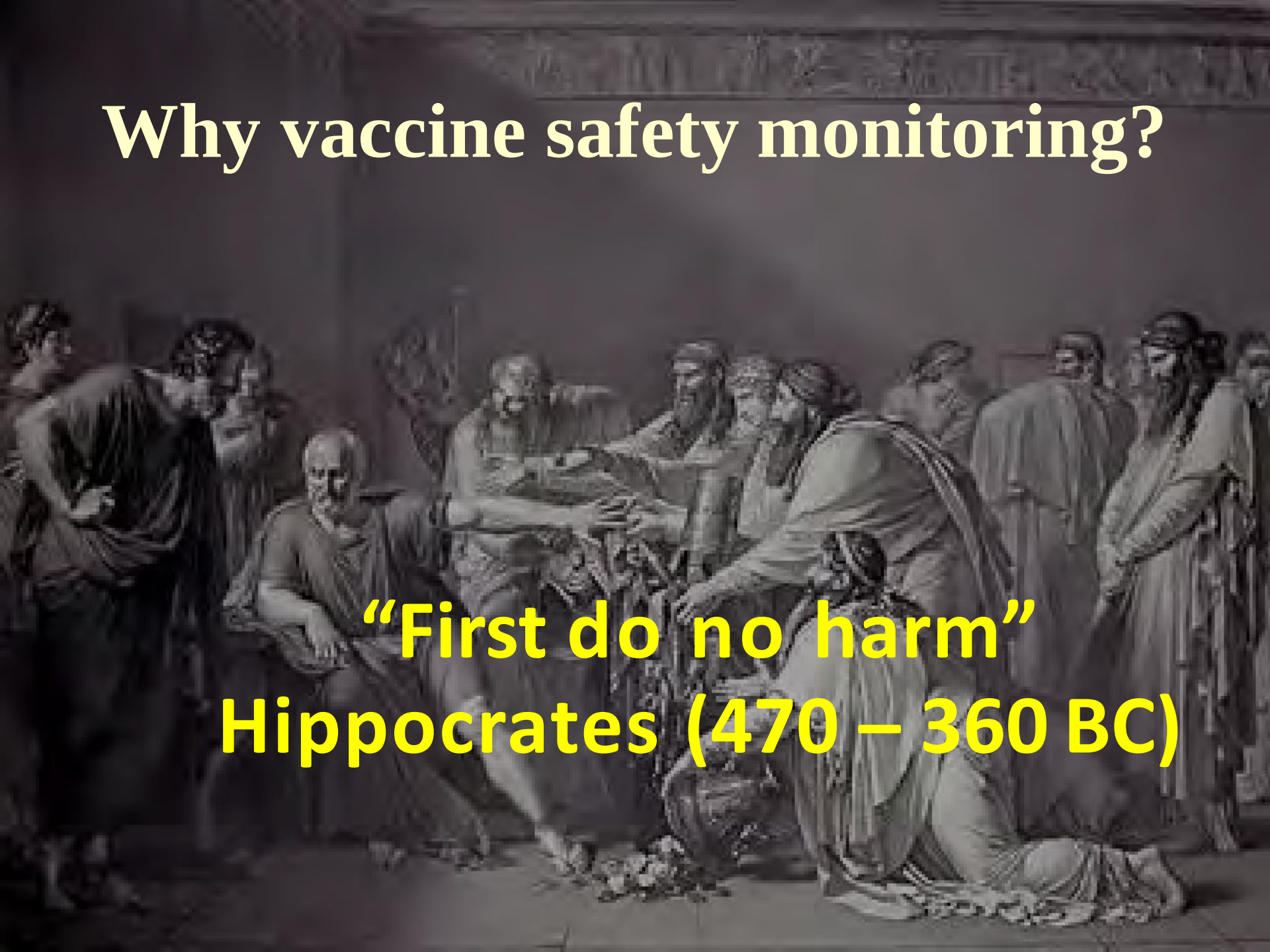
Immunization Safety on New Vaccine Introduction

Severe Allergic Reaction In US Health Worker Minutes After Pfizer Shot

World | Reuters | Updated: December 17, 2020 2:15 pm IST

Immunization is Safe !!!!!!!!!

Why vaccine safety monitoring?



“First do no harm”
Hippocrates (470 – 360 BC)

Goal of ADR/ AEFI surveillance

- The major goal of immunization safety surveillance is early detection and analysis of adverse events and appropriate and quick response in order to decrease the negative impact on the health of individuals and the immunization programme.

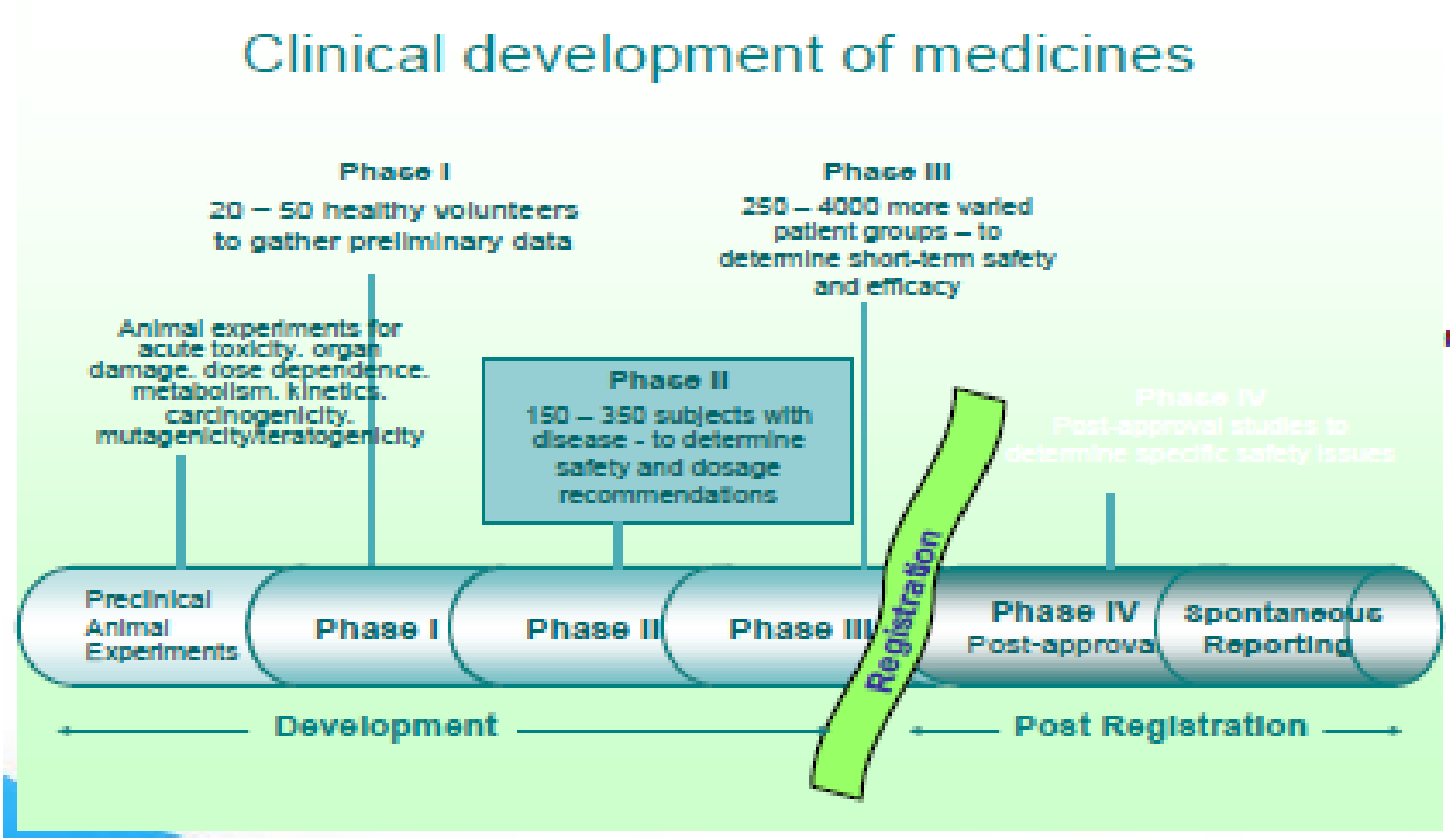
- In establishing immunization safety surveillance, the clear articulation of objectives should generate the support of health workers and encourage them to report AEFI.

Pharmaco-vigilance & Regulatory Action

Pharmacovigilance is the practice of detecting, assessing, understanding, responding to and preventing adverse drug reactions, including reactions to vaccines.

Pharmacovigilance is now an integral part of the regulation of drug and vaccine safety.

Post Marketing Surveillance for Regulatory action



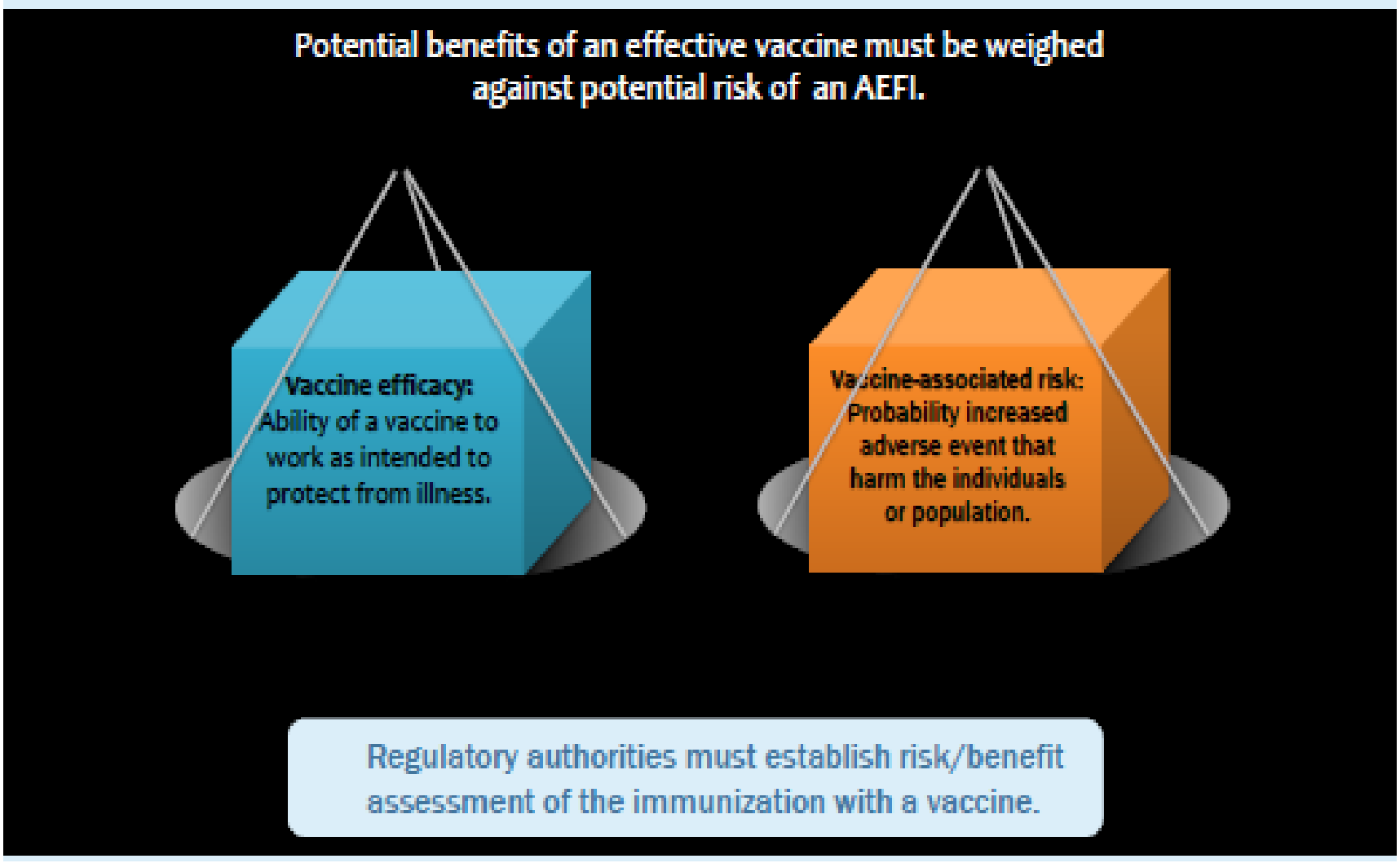
Benefit, risk/harm assessment

Positive effects

Potential harm

- CIOMS IV, 1998

The optimal balance on efficacy and safety of vaccine



The balance: Benefit / Risk assessment

Perception of risk benefit assessment

Immunization Safety Surveillance in India

1. **ADR Surveillance – Through PvPI (Pharmacovilance Program of India by IPC)**
2. **AEFI surveillance - Through UIP (by Immunization Division)**
3. **CDSCO is national regulatory authority for drugs including vaccines.**
4. **All organizations are under MoHFW, Govt of India.**

Section -2

ADR SURVEILLANCE THROUGH PVPI

ADR Surveillance PvPI

- The Pharmacovigilance Program of India (PvPI) was launched with mission to promote patient safety of 1.27 billion people of India.
- Adverse drug Reactions (ADRs) are reported from all over the country to NCC-PvPI, which also work in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden to contribute in the global ADRs data base.
- NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India (CDSCO) in taking decision for safe use of medicines.
- Since its initiation in 2010, the Pharmacovigilance Programme of India (PvPI) has been enriching the quality of performance and expanding its fields activity.

National Monitoring on Vaccine Safety

Partners Roles and Responsibilities in Ensuring Vaccines Safety

Indian Pharmacopoeia Commission National Coordination centre-Pharmacovigilance Programme of India (NCC-PvPI)

1. To monitor, report, collate and analyse adverse events due to medicine & vaccines.
2. AMCs shall be responsible to monitor & reporting of adverse events to NCC-PvPI and also share AEFI-ICSRs with DIO & SEPIO.
3. NCC-PvPI shall be responsible to share AEFI-ICSRs with AEFI Secretariat & CDSCO.
4. Communication of vaccines signals to AEFI secretariat.

Adverse Event Following Immunization (AEFI) Secretariat

ITSU
IMMUNIZATION TECHNICAL SUPPORT UNIT
Ministry of Health & Family Welfare

1. Responsible to coordinate with NCC-PvPI for the management of AEFI-ICSRs.
2. Responsible to coordinate with respective AMC and concerned Zonal Consultant for further follow up with SEPIO/DIO.
3. To perform causality assessment of AEFI cases.
4. To share reported AEFIs with CDSCO.

Central Drugs Standard Control Organization (CDSCO)

1. To ensure safety, efficacy & quality standards of pharmaceuticals, medical devices & vaccines.
2. Regulatory actions are incite by CDSCO in case quality of implicated vaccines to be responsible for adverse events.
3. Enforcement and site inspection where the AEFI occurred.
4. Responsible for taking appropriate regulatory decisions.

Report Serious AEFI Case Notification Form

Serious AEFI Case Notification Form – ADR Monitoring Center*

ICSR No. _____	**Reporting Format No.**
Name & address of ADR Monitoring center (AMC):	
Patient Name	
Age: _____	Sex: Male/Female
Father/Husband's Name	
Complete Address of the Case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*	
P I N -	P H O N E -
Date of Vaccination: __ __/ __ __/ __ __ __ __ Address of health facility where vaccinated (include name of village/urban area, block, DISTRICT and STATE)#:	
Name of vaccines with dose received (if known)	
Date of first symptom (D D M M Y Y Y Y)	Time of first symptom (H H M M) (AM/PM)
Hospitalization:(No/ Yes) Date- (D D M M Y Y Y Y)	Time of hospitalization (H H M M) (AM/PM)
Name and address of hospital (if hospitalized):	CR No./MRD No _____
Current status (encircle)	Death / Still Hospitalized / Recovered & Discharged with sequelae /Recovered completely and discharged / Left Against Medical Advice (LAMA) / Not hospitalized
If died, Date of Death (D D M M Y Y Y Y)	Time of Death (H H M M) (AM/PM)
Describe AEFI (signs and symptoms):	
Name & signature of AMC Coordinator/ Medical officer: Email: Contact No.	
*Date form sent to District Immunization Officer# (where patient was vaccinated)- __ __/ __ __/ __ __ __ __	
*Date form sent to State Immunization Officer# (where patient was vaccinated)- __ __/ __ __/ __ __ __ __	
*Date form sent to PVPI, Ghaziabad- __ __/ __ __/ __ __ __ __	
*Date form sent to Immunization Division / AEFI Secretariat (aefiindia@gmail.com)- __ __/ __ __/ __ __ __ __	
Name & signature of Pharmacovigilance Associate: E mail: Contact number:	

#The case is to be notified to the DIO of the district where the vaccine was administered.
***This form should be scanned and emailed simultaneously to DIO, SEPIO, PVPI and AEFI Secretariat.**

The case is to be notified to the DIO of the district where the vaccine was administered.

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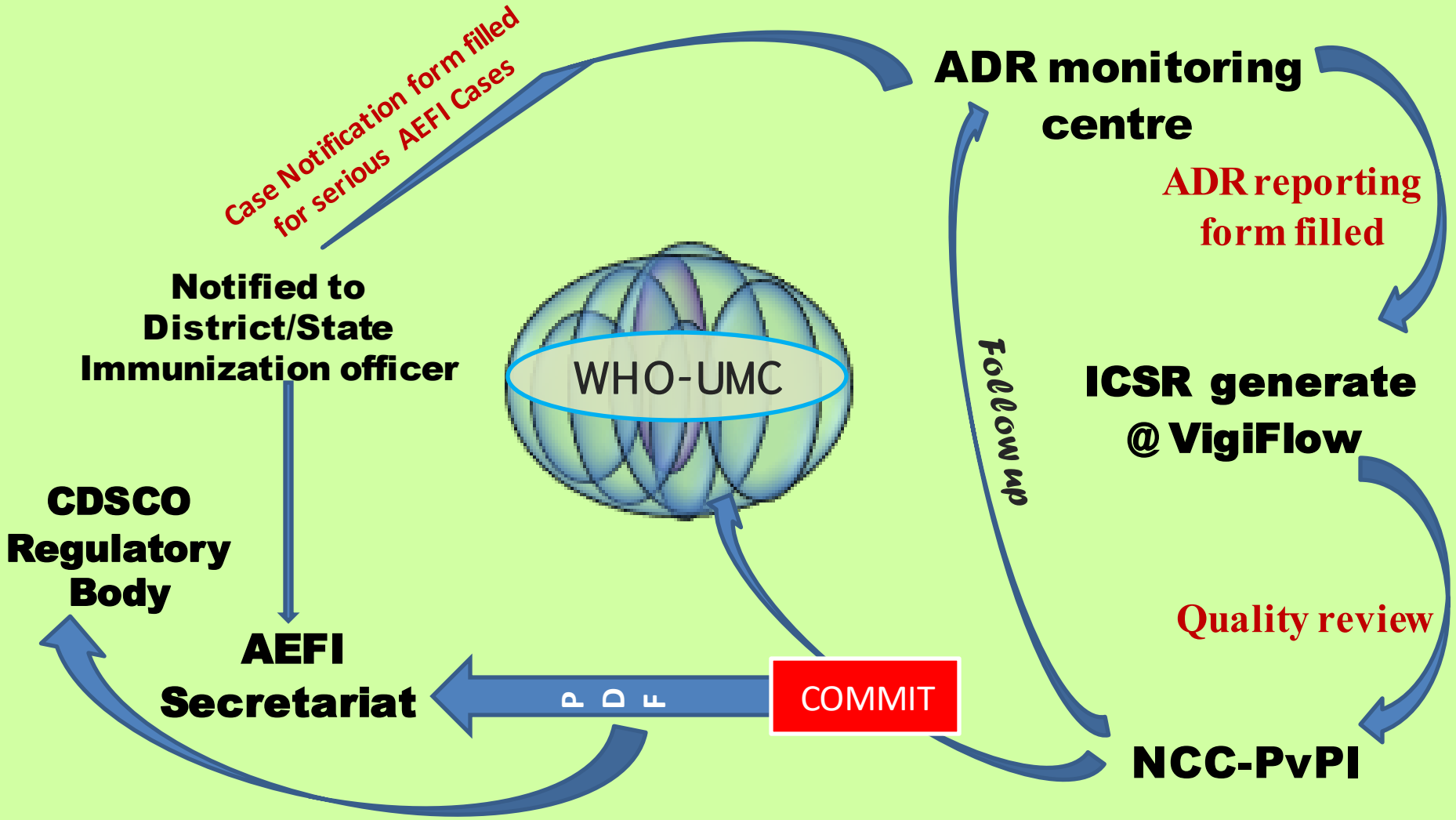
AEFI-ICSR Reporting System



ADVERSE DRUG REACTION (ADR) REPORTING IN INDIA

HOW INDIAN POPULATION GETTING BENIFITED...

ADR Monitoring Center (s) [AMC's]

Safety Alerts Communication

Healthcare Professionals, Patients or Others, may report ADR either directly to the NCC-PvPI OR AMC's via Mobile App or Toll Free Number

Reporting Tools

Toll Free Number 1800-180-3024

Pharmaceutical Industries

NCC-PvPI

Case Processing/ Quality Review

Case Reverted

Invalid/ Incomplete Report

Case Reverted

Valid/ Complete Report

Uppsala Monitoring Centre

Global safety data collection

Causality assessment & data mining of reports

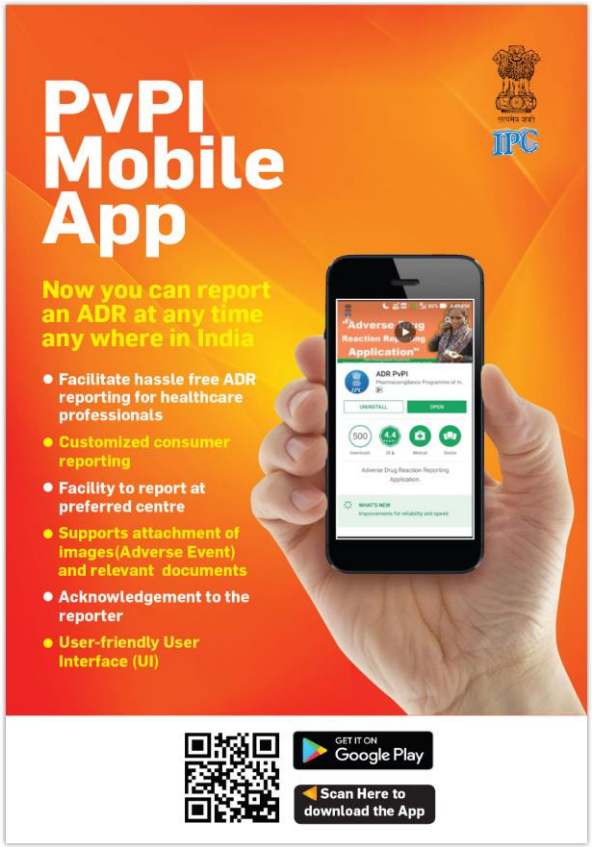
CDSCO

Regulatory action

Signal

Reporting Tools for the Stakeholders

ADR PvPI in
Google play store



1800 180 3024

ADR Data entry to VigiFlow

NCC PvPI data to promote patient's safety

Drug Alert

Change in Package insert

Signal

Drug Alert	Updating Package insert	Signal
76	38	05

Regulatory Matters Reflected in WHO Newsletter

World Health Organization

WHO Pharmaceuticals NEWSLETTER

2016 No.5

Antirabies vaccine

Risk of erythema multiforme

India. The National Coordination Centre - Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission (IPC, NCC-PvPI) has requested the revision of the drug safety label for antirabies vaccine to include erythema multiforme as a potential risk.

Antirabies vaccine is indicated for active immunization against rabies, both as prophylaxis and post bite cases.

NCC-PvPI has received two reports of erythema multiforme with exposure to

Section 3

AEFI SURVEILLANCE THROUGH UIP

Revised National Immunization Schedule

Age	Vaccines given
Birth	BCG, OPV-0, Hepatitis B Birth dose
6 Weeks	OPV-1, Pentavalent-1, fIPV-1, Rota-1 & PCV-1
10 weeks	OPV-2, Pentavalent-2 & Rota-2
14 weeks	OPV-3, Pentavalent-3, fIPV-2, Rota-3 & PCV-2
9-12 months	MR-1, JE1*, PCV-Booster
16-24 months	MR-2, JE2*, DPT-Booster 1, OPV- Booster
5-6 years	DPT-Booster 2
10 years	Td
16 years	Td
Pregnant Mother	Td1, 2 or Td Booster**

* *in endemic districts only*

** *one dose if previously vaccinated within 3 years*

Being introduced/scaled up

Universal Immunization Programme

(Scope and scale)

2.6 crore newborns & 3 crore pregnant women targeted annually, ~9 million immunization sessions annually

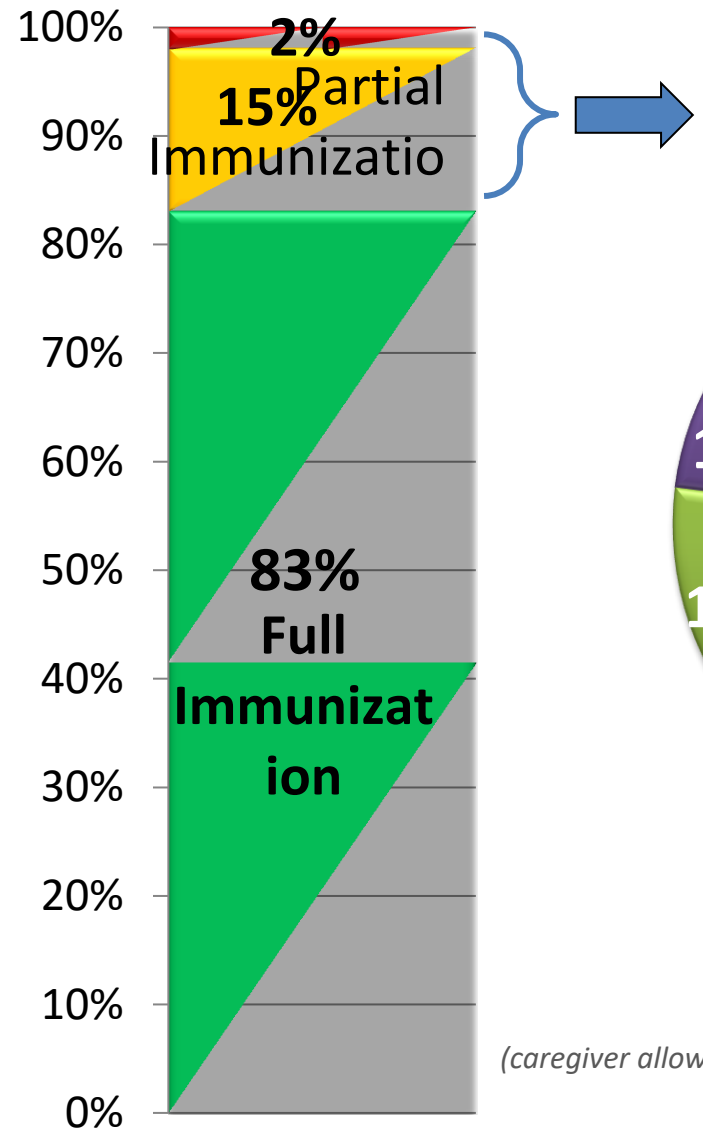
8 vaccines nationally- BCG, DPT, OPV, IPV, Measles, Hep B, Tetanus, Pentavalent
4 vaccines- Measles-Rubella, Rotavirus, PCV, JE in select states/districts

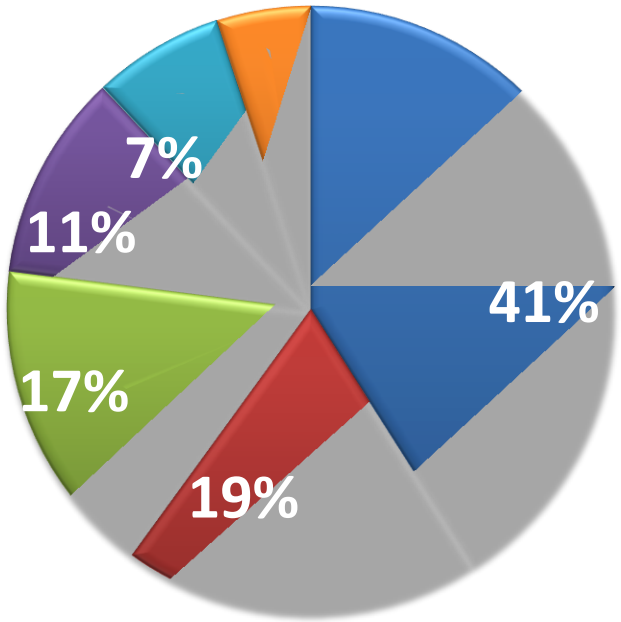
One of the largest public health programs in India

90 lakh sessions planned per year; >27,000 cold chain points for storing and distributing vaccines

India is the largest manufacturer of vaccines with a functional National Regulatory Authority

Immunization status of children in India-2018*
Reason why children are missed





- Awareness & Information gap
- AEFI apprehension
- Operational gap
- Child travelling
- Others
- Refusal

N = 65,475

(caregiver allowed multiple responses ; grouped under various heads)

Number of children monitored = 1,45,947

Source : RI concurrent monitoring data 2018 (Jan'18-July'18)

Why do we need an AEFI surveillance system?

1. *To recognise programme [illegible] proper storage, handling [illegible] vaccines)*
2. *To [illegible] ts co[illegible], do[illegible], pa[illegible] vaccine con[illegible]*
3. *To c[illegible]ure, serious AEFIs undetectable during clinical trials*

- Maintaining vaccination Confidence
- Stopping false blames on vaccine
- Identifying and correcting immunization program errors
- Detect new signals

AEFI Surveillance

AEFI system is NOT meant

to blame field staff

but rather to improve the overall quality of immunization services

Definition of AEFI

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

The adverse event may be any unfavorable or unintended sign (e.g. Abscess following vaccination), abnormal laboratory finding (e.g. Thrombocytopenia following measles vaccination) symptom or disease (e.g. Disseminated BCG infection following BCG vaccination).

AEFI Surveillance

- Adverse event may be a clinical symptom, unfavourable/ unintended sign, abnormal lab finding, disease condition.

Types of AEFI Cases

1 Minor

- 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).

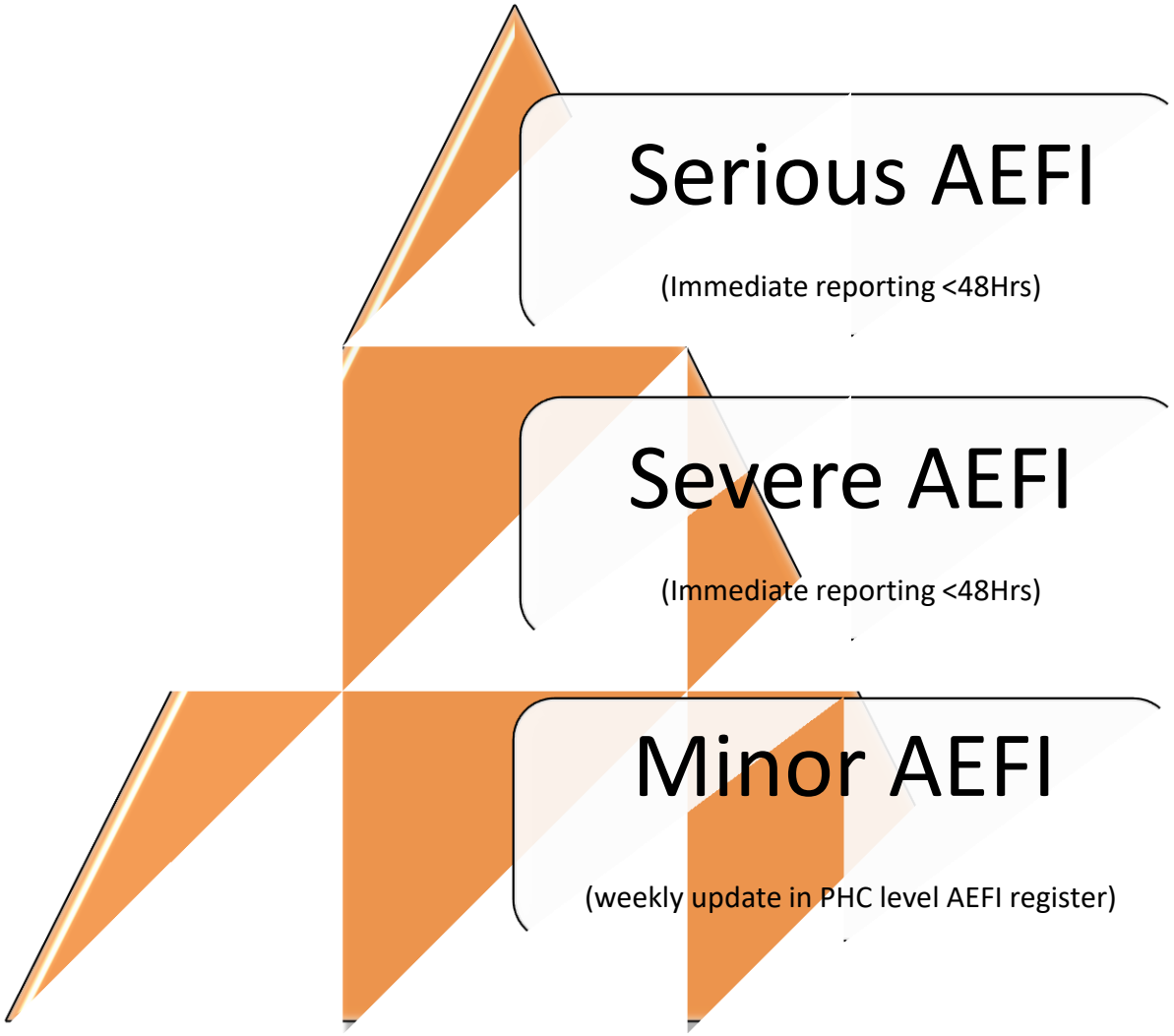
2 Severe

- Can be disabling and, rarely life threatening
- Most do not lead to long-term problems
- Must be reported
- Examples of severe reactions include
- Non - hospitalized cases of anaphylaxis that has recovered, high fever(>102 degree F), ypotonic hyporesponsive episodes, sepsis etc

3 Serious

- Death.
- Hospitalization
- Results in persistent or significant disability.
- AEFI cluster
- Community / media / parental concern

Types of AEFI Cases



Minor AEFIs

- **Common, Self-limiting** e.g. pain & swelling at injection site, fever, irritability, malaise, etc.
- Treat symptomatically – paracetamol, cold sponging
- Assure parents & care givers
- Record AEFIs in block/PHC AEFI register; report monthly in HMIS
- Report and investigate minor AEFIs in clusters as serious/severe AEFIs
- Paracetamol, at a dose of up to 15 mg per kg every 6-8 hours with a maximum of four doses in 24 hours, is useful for common minor reactions; it eases pain and reduces fever.

Severe and Serious AEFIs

- Severe AEFIs
  - Increased severity of minor AEFIs; do not lead to long-term problems; rarely life threatening; can be disabling
  - Non-hospitalized cases

  Examples: Non-hospitalized cases of anaphylaxis that has recovered, high fever (>102 degree F), hypotonic hyporesponsive episodes, sepsis, etc.

- Serious AEFIs
  - Deaths
  - Hospitalizations
  - Clusters
  - Disability
  - Media reports/ Community/ parental concern

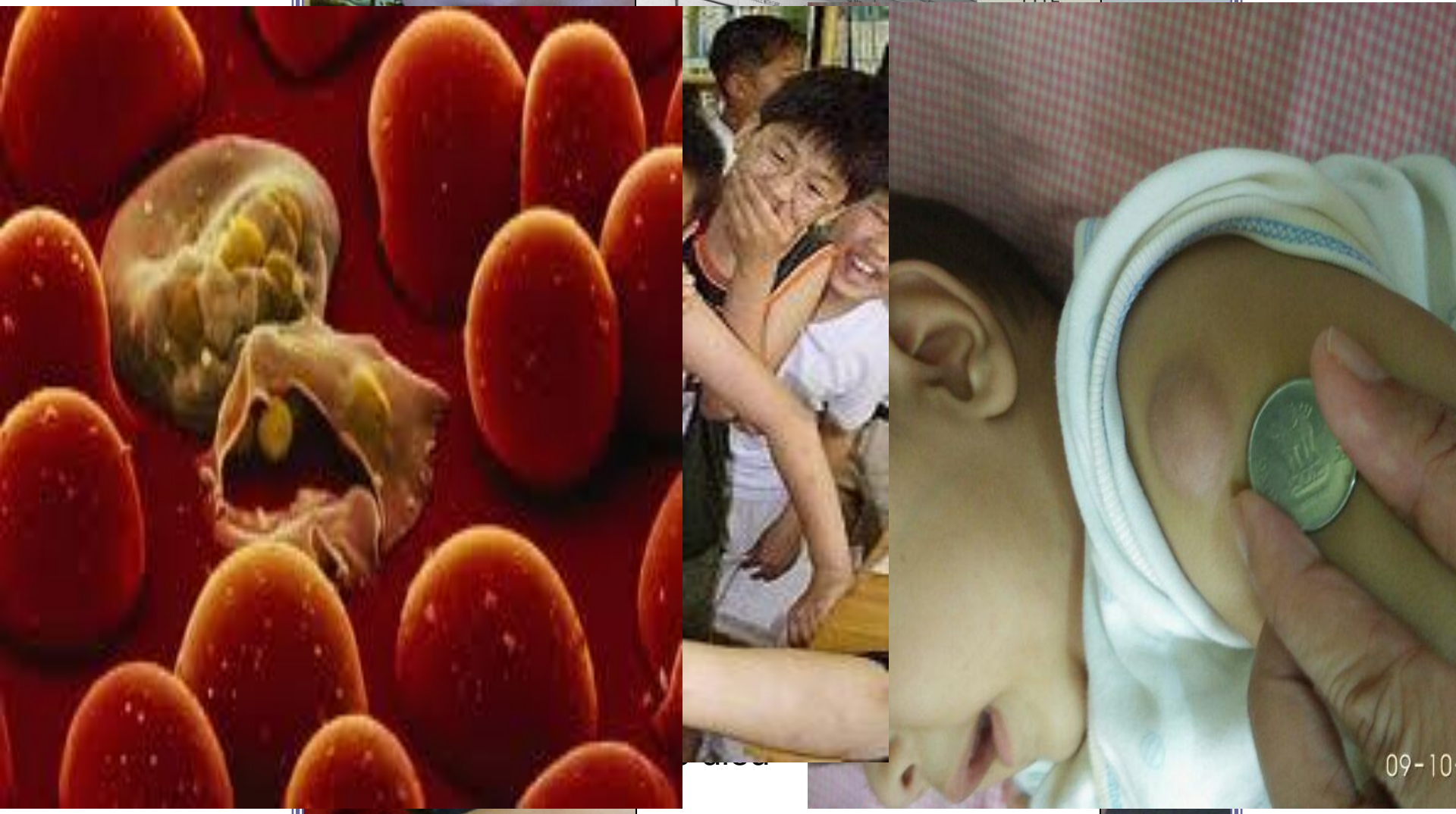
Report all serious and severe AEFIs immediately in Case Reporting Formats (CRFs)!

Cause Specific Classification of AEFI Cases*

1 Vaccine product-related reaction	2 Vaccine quality defect-related reaction	3 Immunization error-related reaction	4 Immunization anxiety-related reaction (Including Immunization Triggered Stress Response)	5 Coincidental event
An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.	An AEFI arising from anxiety about the immunization.	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

* CIOMS / WHO 2012

WHO cause specific definition of AEFIs



Immunization anxiety-related reaction

- Also called as Immunization Triggered Stress Response
- More common in older children
- Fainting (vasovagal syncope or syncope)
- Hyperventilation
- Seizure like movements
- headache, dizziness, tingling around the mouth and in the hands
- Vomiting, Breath-holding spells
- Needle-phobia,
- Hysteria, itching, weakness of limbs

What are potential causes for immunization error related reactions?

Non sterile injection

Reconstitution error

Injection at incorrect site

Vaccine transported/ stored incorrectly

Contraindication ignored

Immunization error-related reaction

- Immunization safety is the process of ensuring and monitoring the safety of all aspects of immunization, including vaccine quality, adverse events, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
- Preventable AEFIs

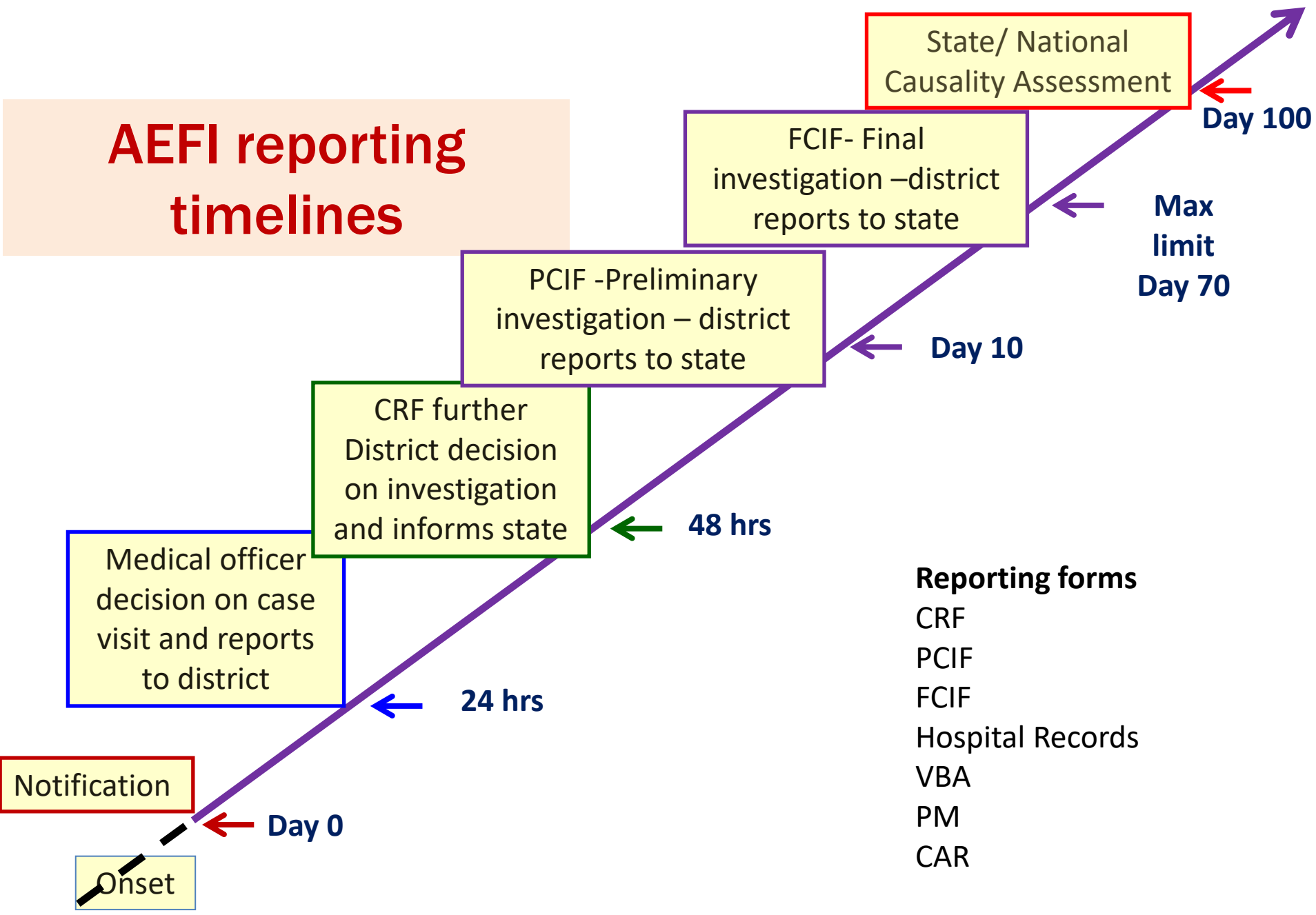
Which adverse events should be reported?

1. Severe and Serious AEFI cases
2. Signals and events associated with a newly introduced vaccine or new clinical sign/ symptom
3. AEFI that may have been caused by an immunization error
4. Significant events of unexplained cause occurring within 30 days after vaccination
5. Events causing significant parental or community concern and media concern.

Basics of AEFI Surveillance

1. **Detection of AEFI:**
   - Follow up by ANM after vaccination/ PHC-MOs/ AEFI cases treated by clinicians at tertiary care hospitals
2. **Recording of AEFI**
   - PHC AEFI Register, HMIS, VPD surveillance, RCH online
3. **Reporting of AEFI**
   - CRF form with 48HRS through DIO/ DRCHO SAFEVAC online
   - ADR PvPI Mobile app (by individual clinicians)
   - Toll free Number : 1800 180 3024 (by individual clinicians, patients)
4. **Investigation of AEFI**
   - PCIF <10days, FCIF, VBA, Hospital Records, PM reports
5. **Causality assessment**
   - By State AEFI Committee and National AEFI Committee
6. **Corrective actions**
   - District/ State/ National

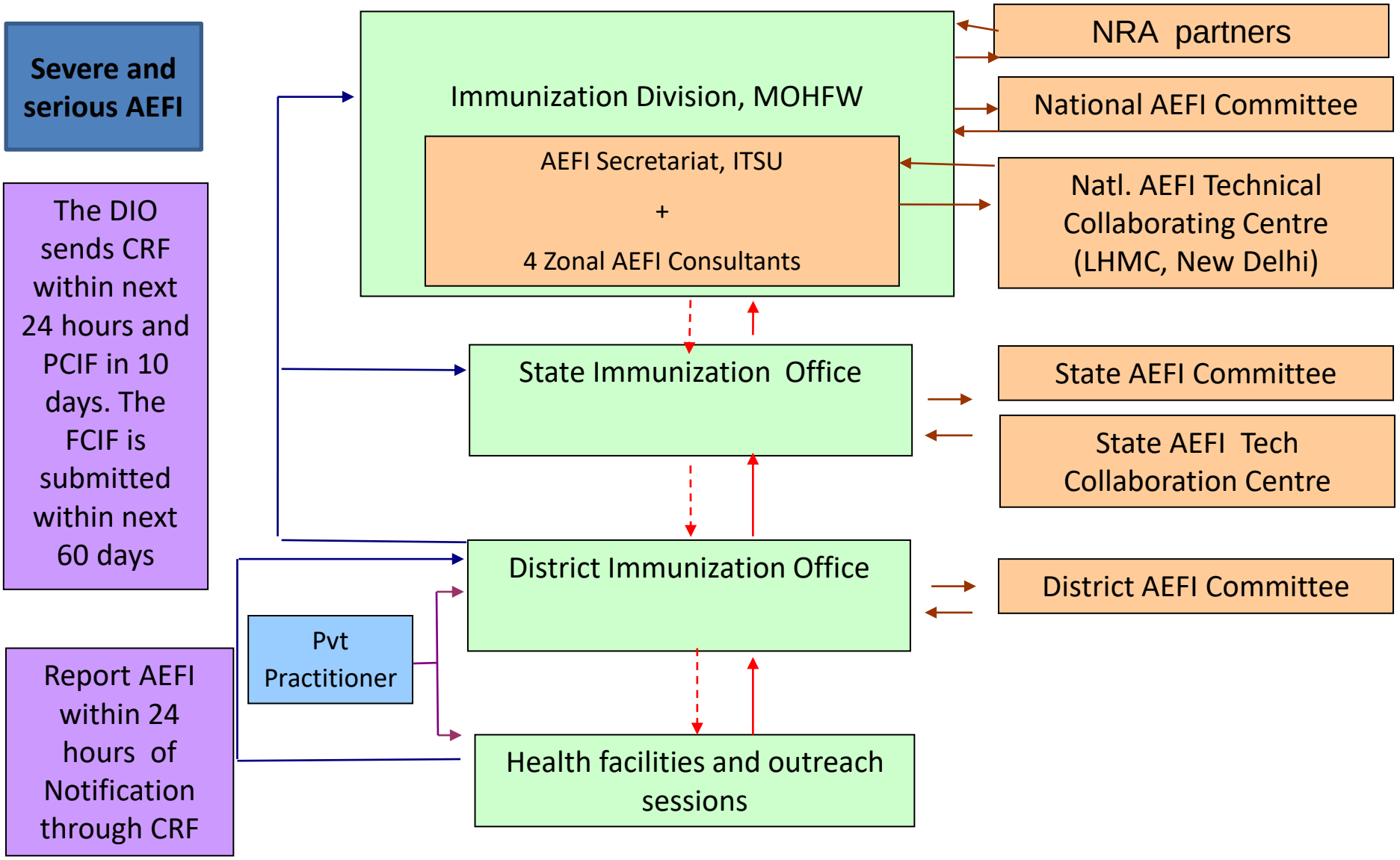
AEFI reporting timelines



Reporting forms

CRF
PCIF
FCIF
Hospital Records
VBA
PM
CAR

AEFI Organizational Structure



District / State/ National AEFI Committees

Composition

- **Pediatrician, (Chairperson)**
- **Epidemiologist/Public Health Specialist**
- **Representative from Drug Authority**
- **Physician, Microbiologist, Pathologist, Forensic Expert, Neurologist**
- **Cold Chain officer**
- **Member Infectious Disease Surveillance Program(IDSP)**
- **Representative from local bodies like corporations**
- **Representatives from professional bodies like IAP, IMA**
- **Representatives from partners agencies WHO, UNICEF**
- **Pharmacologist from -ADR Monitoring Centre under PvPI**

Terms of reference

(national/state/district)

- Strengthen and validate AEFI reporting at all levels
- Ensure implementation of uniform standards and formats.
- Prompt & thorough investigation of serious AEFIs and periodic review of non serious AEFIs
- Timely classification of cases
- Causality assessment (*Brighton Classification*)
- Support spokesperson for media interface and management.

Member Secretary: State/ District Immunization Programme Officer

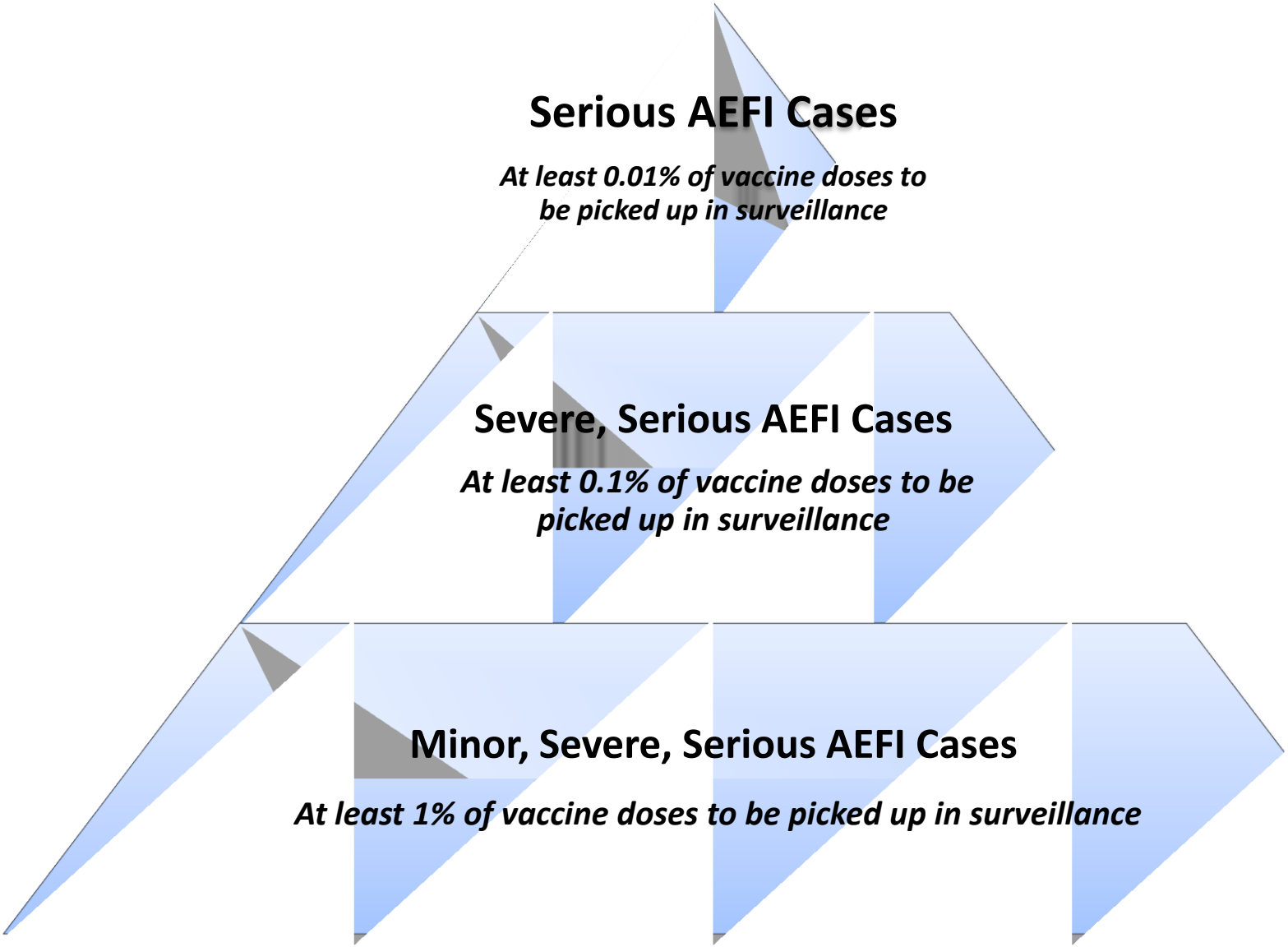
How frequent AEFI cases may occur?

TABLE 3. FREQUENCY OF OCCURRENCE OF REPORTED ADVERSE REACTIONS

Frequency category	Frequency in rate	Frequency in %
Very common	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1000 and < 1/100	≥ 0.1% and < 1%
Rare	≥ 1/10 000 and <1/1000	≥ 0.01% and < 0.1%
Very rare	< 1/10 000	< 0.01%

*Source: Global manual on surveillance of AEFI by WHO

AEFI Surveillance System



Reporting Tools for AEFIs

CRF has to be reported to District Immunization Officer further to state / nation

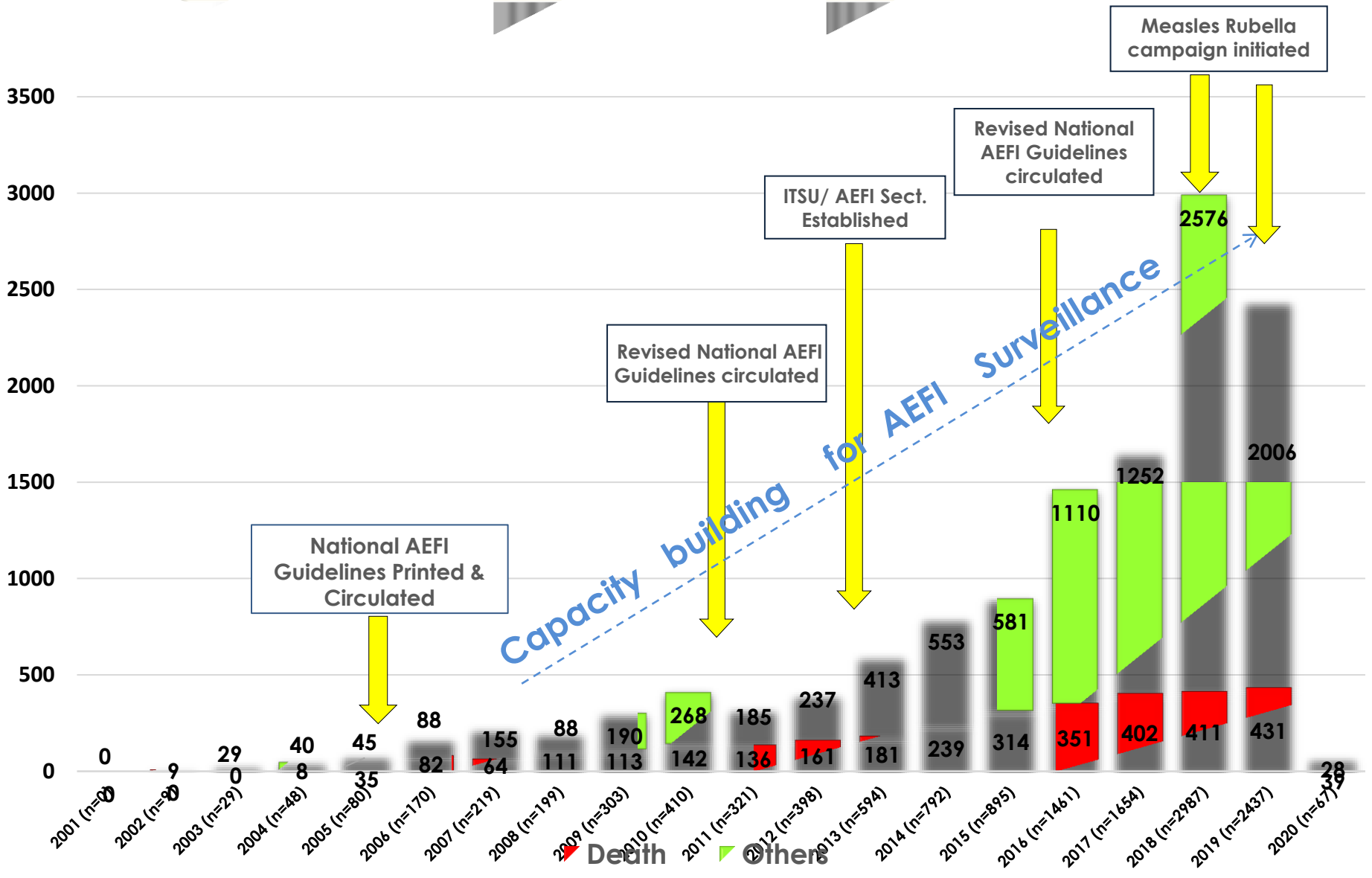
District can report through online www.safevac.nhp.gov.in

SAFE-VAC

Surveillance and Action For Events following vaccination

Through Email : aefiindia@gmail.com to Deputy Commissioner (UIP) National AEFI Secretariat

Overview of National AEFI Surveillance (AEFI Cases Reported 2001-2020*)



Data as on 31-Jan- 2020 (as per DOV)

AEFI Causality Assessment 4 Steps:

- **Step 1. Eligibility:** to determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.
- **Step 2. Checklist:** to systematically review the relevant and available information to address possible causal aspects of the AEFI (Annex I).
- **Step 3. Algorithm:** to obtain direction as to the causality with the information gathered in the checklist.
- **Step 4. Classification:** to categorize the AEFI's association to the vaccine/vaccination on the basis of the direction determined in the algorithm.

WHO Cause Specific AEFI Classification

A. Consistent causal association to immunization

A1. Thrombocytopenia after MMR vaccination

A2. Paralytic polio caused by incomplete IPV inactivation

A3. Transmission of infection by contaminated multidose vial

A4. Vasovagal syncope in an adolescent following vaccination

B. Indeterminate

B1. Irritable bowel syndrome after TT vaccine (hypothetical and unproved so far)

B2. Thrombocytopenia after MMR vaccine in a dengue endemic area

Example

C. Inconsistent causal association to immunization

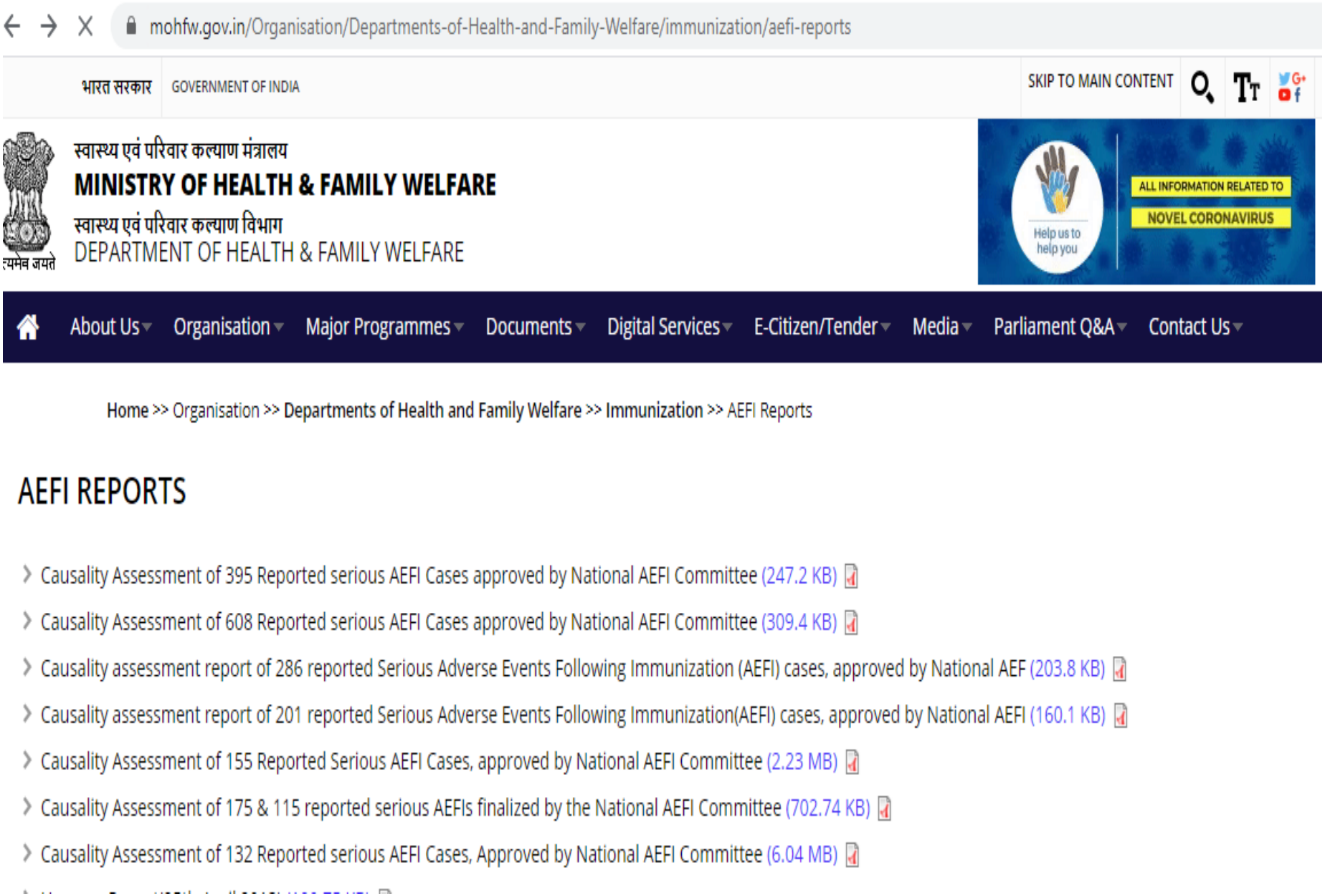
C. Coincidental

Child dies after DPT vaccine and autopsy shows congenital heart disease

or

Fever occurs after vaccination (temporal association) and malarial parasite isolated from blood

Improved causality assessment



Corrective Actions and follow-up to AEFI

- Patient care, preparedness : Anaphylaxis, 108 ambulance service, quick referral

- Immunization error-related: Correct the cause of the error. changing logistics for supplying the vaccine; changing procedures at the health facility; training of health workers; intensifying supervision. Whatever action is taken, it is important to review at a later date to check that the immunization error-related events have been corrected.

- Coincidental Events : Harm the immunization programme through false blaming on vaccination program attribution is immense.

- Vaccine-related reaction: if higher reaction rate than expected from a specific vaccine or lot, obtain information from the manufacturer withdrawing that lot; vaccine vial testing, investigating with the manufacturer; obtaining vaccine from a different manufacturer

Summary of Immunization Safety Surveillance System

ADR Surveillance (PvPI)

- Both drugs and vaccines
- PvPI ADR monitoring centres are reporting vaccine ADRs through Vigiflow software to global Pv database - CNF (Case Notification Form) and Vigiflow generated ICSR(Individual Case Safety Report)
- AMCs are also responsible to report vaccine ADRs to NCC-PVPI and DIO, SEPIO National AEFI secretariat.
- Types : Serious and Non serious AEFIs
- **MedDRA Classification is being used. (Med**ical **D**ictionary for **R**egulatory **A**ctivities)
- Preliminary CA is done at the time of reporting**.**

AEFI Surveillance (UIP)

- **Only for vaccines - UIP & Non UIP vaccines both public vaccinations and private vaccinations**
- **AEFI surveillance** districts are reporting AEFI through CRF (Case Reporting Form) to state & national through https://safevac.nhp.gov.in.
- Types : Minor, Severe, and serious AEFIs. Severe & serious AEFI to be reported with 48hrs.
- **Brighton's case definitions are used for clinical sign/ symptom**.(standardized case definitions for AEFI)
- **WHO Cause Specific Classification is being used in CA.** State & national level AEFI committee with group of technical experts are doing CA.

CDSCO is national drug regulatory authority for drugs including vaccines to take appropriate action.

Summary of WHO Vaccine ADRs Rates

WHO Vaccine Adverse Drug Reactions Rates

(Reference: WHO vaccine reaction rates information sheets) https://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

Name of Vaccine & Type of ADR	Name of Adverse Drug Reactions	Frequency of Adverse Drug Reactions per doses given
BCG vaccine / Mild ADRs	Injection site papule (onset 2-4 weeks) Mild ulceration (1-2 months) Scar (2-5 months)	Almost all vaccinees
BCG vaccine / Severe ADRs	Local : Local abscess, Keloid, Lymphadenitis Suppuration (onset 2-6 months)	1 per 1,000-10,000
BCG vaccine / Severe ADRs	Systemic: (1-12 months onset time) Cutaneous skin lesions Osteitis, Osteomylitis Disseminated BCG disease Immune Reconstitution Syndrome	Case reports 1 per 3,333 – 10^8 1 per 230,000 – 640,000 1 per 640,000
DPT vaccine / Mild ADRs	Local reactions (50%) Systemic reactions such as fever over 38°C and irritability (40% to 75%), drowsiness (33% to 62%), loss of appetite (20% to 35%), vomiting (6% to 13%) Local redness, 37.4% local swelling, 40.7%; pain, 50.9%; fever, 31.5%; drowsiness, 31.5%; fretfulness, 53.4%; vomiting, 6.2%; anorexia, 20.9% Persistent inconsolable crying, 3.1%.	
DPT vaccine / Severe ADRs	High fever.	0.3%
DPT vaccine / Severe ADRs	Persistent crying.	3.5%
DPT vaccine / Severe ADRs	Seizure, Febrile seizures occurring within 3 days	60 per 100,000 doses
DPT vaccine / Severe ADRs	Hypotonic–Hyporesponsive episode (HHE).	291 per 100,000 Doses (57-250 per 100,000 doses)
DPT vaccine / Severe ADRs	Encephalopathy.	0.3 – 5.3 per 1,000,000 doses. 1 per 310,000 to 5,300,000 doses

WHO Vaccine safety basics course

WHO Course : Investigation of AEFI

- Global Vaccine Safety
- Global Vaccine Safety Initiative
- Global Advisory Committee on Vaccine Safety
- Reference documents and publications

WHO E-Learning course: Investigating Adverse Events Following Immunization

WHO

Acknowledging that the cause of a large proportion of AEFI cannot be established by AEFI causality assessment committees due to incomplete AEFI investigation, WHO is launching an E-learning course on AEFI investigation to learn: 1) when to launch an investigation 2) what information is required to successfully complete an investigation and 3) how to successfully manage inter-personal communication with relevant stakeholders.

Learn at your own pace with a highly interactive course, with a combination of informative content and immersive scenarios where you will be called upon to investigate serious AEFI in different parts of the world. Following a successful course completion, you will be able to download a course certificate.

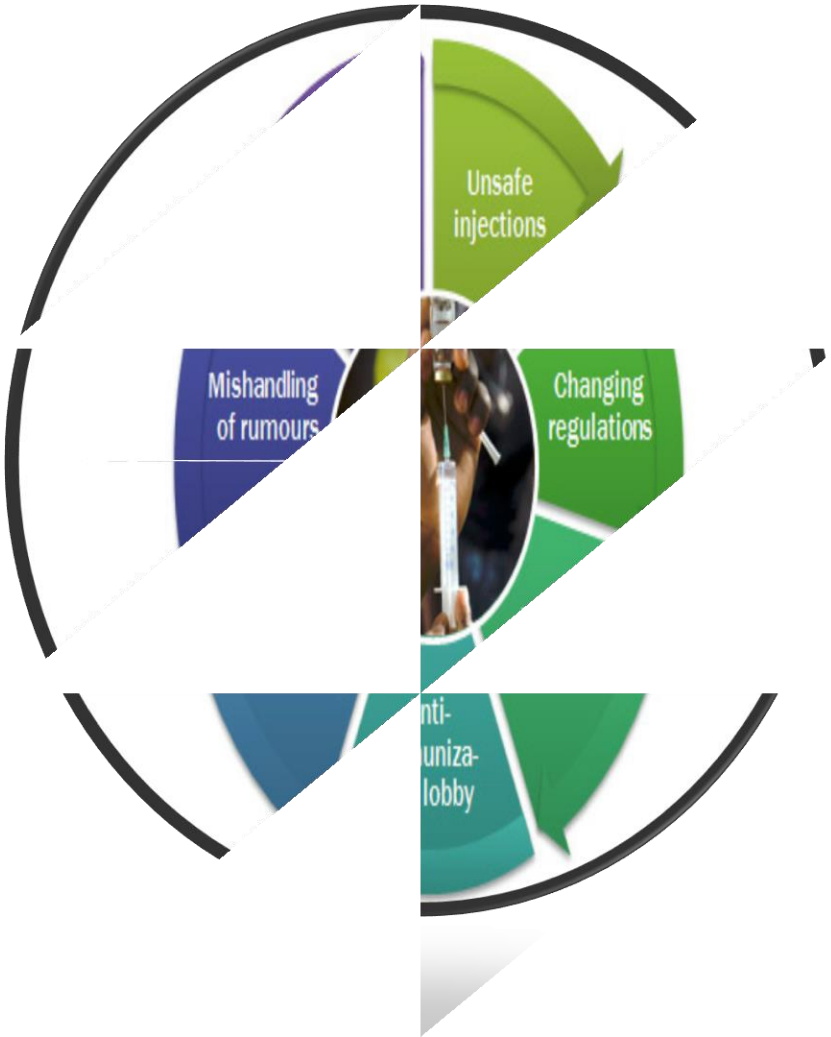
WHO software guide for AEFI Causality Assessment

Global Vaccine Safety

- Global Vaccine Safety
- Global Vaccine Safety Initiative
- Global Advisory Committee on Vaccine Safety
- Reference documents and publications

A software to guide AEFI causality assessment

Conclusions on Vaccine Safety Surveillance



- Vaccine Pv is an important part of vaccine regulation.
- The vaccine product and the process of vaccination must be considered in vaccine Pv.
- Methods for vaccine Pv need to evolve in line with technological advancements and the production of new vaccines

Challenges in Immunization Safety Surveillance

- 2 parallel surveillance system on ADR/ AEFI not integrated.
- All serious, severe AEFI needs to be reported in PvPI so that it goes to UMC-WHO data repository for monitoring safety purposes.
- WHO aims to ensure medicines, vaccines and other health products for supply to low-income countries are quality-assured, safe, effective and accessible to all populations.
- Weak surveillance reporting in ADR, AEFI with reference to given volume of vaccine doses in country.

Role of IIHMR in Immunization Safety Surveillance

- Techno managerial support for states immunization safety surveillance committees
- Look for partnership with PvPI ADR monitoring centers (only medical college hospital or large tertiary care hospitals) for research proposals & training.
- Partnership with Pharma companies for post marketing surveillance on ADR for new drug
- Covishield, Covaxin – explore new covid19 vaccine introduction research opportunities
- PGDM Pharmaceutical Management specialization can be included a module on ADR surveillance & drug safety signal detection.


THANKS

Q & A