Ministry of Health & Family Welfare
Government of India

NATIONAL HEALTH MISSION

AEFI ADVERSE EVENT FOLLOWING IMMUNIZATION

Surveillance and Response

OPERATIONAL GUIDELINES

2024

AEFI ADVERSE EVENT FOLLOWING IMMUNIZATION Surveillance and Response

OPERATIONAL GUIDELINES

2024

Apurva Chandra
Secretary

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
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Message

For the past many decades, the Government of India's Universal Immunization Program (UIP) has been providing life-saving vaccines to protect the largest cohort of eligible beneficiaries (approximately 27.4 million children and 30 million pregnant women) in the world from vaccine preventable diseases (VPD). In 2021, India launched the world's largest vaccination campaign to protect its citizens against the COVID-19 pandemic. More than 2.2 billion doses were administered across the country using indigenously manufactured vaccines. Additionally, to ensure coverage of routine immunization during COVID-19, India conducted targeted catch-up campaigns IMI 3.0, IMI 4.0 and IMI 5.0 in 2021, 2022 and 2023 respectively.

As one of the largest manufacturers and the largest consumer of vaccines in the world, it is important to strengthen the Adverse Events Following Immunization (AEFI) Surveillance programme to demonstrate that all vaccines manufactured and used in the country and exported to other countries are safe.

The COVID-19 pandemic threw a challenge which was taken as an opportunity to improve immunization programme and the vaccine safety surveillance programme. COWIN ensured that vaccination details of each beneficiary are recorded and online certificates are generated. For the first time, India has an electronic AEFI database with minor AEFIs as well as a dedicated signal management system for vaccines.

I am thankful to all the experts who contributed to the development of AEFI Surveillance and Response Operational Guidelines-2024. I hope this guideline will further enhance the capacity and capability of our health workforce to contribute to high quality vaccine safety surveillance programme.

Dated 6th January, 2024

(Apurva Chandra)

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आज़ादी का अमृत महोत्सव

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MESSAGE

The Ministry of Health and Family Welfare, Government of India has intensified efforts in the last few years to improve immunization coverage and quality of immunization services being provided to children and pregnant women. New vaccines and booster doses have been introduced. Several initiatives such as Mission Indradhanush, Gram Swaraj Abhiyan, Intensified Mission Indradhanush and introduction of newer vaccines (rotavirus vaccine, pneumococcal vaccine and measles rubella vaccines) have been undertaken to increase vaccine coverage among the target beneficiaries.

While vaccines undergo stringent clinical trials before being introduced into the programme, a strong post marketing surveillance will ensure that quality of vaccines is maintained. Therefore, having a strong AEFI surveillance system is important to ensure the quality and safety of vaccines in the country.

Over the last few years, several initiatives have been undertaken to strengthen the AEFI surveillance system in the country such as the implementation of a software (SAFE-VAC) for reporting serious and severe AEFIs, introduction of quality management system for AEFI surveillance, ranking of states through key performance indicators, etc.

I am delighted that the AEFI Surveillance and Response Operational Guidelines-2024 has been revised in accordance with the global guidelines for vaccine safety. I thank all the expert members of the National AEFI committee, CDSCO, IPC, Immunization Technical Support Unit (ITSU) and WHO for their contribution in revision of the guidelines. I hope this brings about sustainable improvement in the AEFI surveillance system and enhance vaccine safety in the country.

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GOVERNMENT OF INDIA
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FOREWORD

India's Universal Immunization Programme (UIP) is one of the largest public health programmes in the world. Routine immunization services are provided to 27.4 million birth cohort and 30 million pregnant women each year through 13.6 million immunization sessions spread across the country.

A lot of changes have been made to the UIP with introduction of new vaccines, and booster doses since the last revision of national AEFI Surveillance Guidelines in 2015. Due to COVID-19 vaccination, many improvements have been made to the AEFI surveillance programme.

Some of the changes are allowing vaccinators to use one dose of injection adrenaline at the session site to manage anaphylaxis, dispensing syrup paracetamol instead of tablets after vaccinating infants to manage fever, use of software for reporting of AEFIs (SAFE-VAC - Surveillance and Action For Events following Vaccination), changes to include reporting of AEFIs following adult vaccines, and expansion of Quality Management System for AEFI to states and districts, etc.

I commend the experts who have worked on the Operational Guidelines for Surveillance and Response of AEFI-2024 and hope these revised guidelines will be useful in improving the efficiency of AEFI surveillance activities and contribute towards enhancing the quality of immunization services at all levels.

(Dr. P. Ashok Babu)

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PREFACE

Adverse Events Following Immunization (AEFI) is a critical component of India's Universal Immunization Programme. The success of any national vaccination program hinges not only on the implementation of the vaccination process but also on the robust monitoring of any potential adverse event following the immunization. The data generated through vaccine safety surveillance helps in ensuring that vaccines used in the country are safe. As new vaccines are introduced into the programme, the AEFI surveillance system needs to be constantly improved.

Many changes have been incorporated into the vaccine safety surveillance programme since 2015 when the guidelines were revised last. Vaccinators have been permitted to use injection adrenaline for early management of suspected anaphylaxis. Dispensing of paracetamol syrups at vaccine session sites instead of tablets have ensured the correct dose of paracetamol can be administered to an infant post vaccination. COWIN has demonstrated that reporting of even minor adverse events by vaccinators and serious and severe AEFIs by doctors and vaccine recipients is possible if they have access to the reporting system. Post mortem guidelines have been updated for improved quality of investigations.

The AEFI committees have been expanded to include physicians, obstetricians-gynaecologists, neurologists and cardiologists, for strengthening AEFI surveillance for adult vaccinations. Quality management systems for AEFI surveillance is being rolled out to states, districts and sub-district levels to ensure steady but incremental improvements

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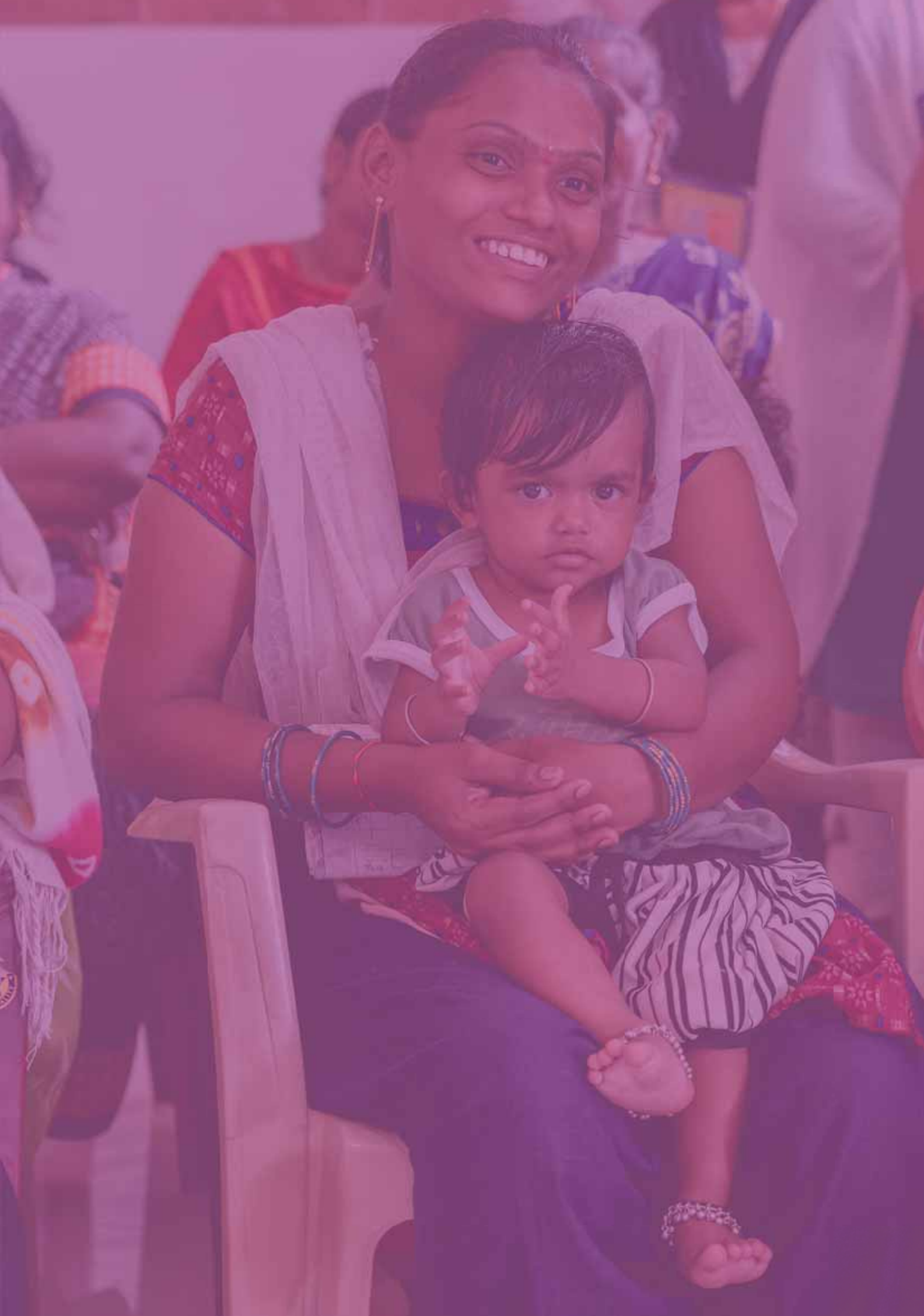
to the surveillance system processes. Exclusive signal management processes for vaccines have been set up to assess potential adverse events which were not previously known to be related to vaccines. There are new chapters on signal management of vaccines; preparations needed for introduction of new vaccines and future pandemics; and AEFI surveillance for adult vaccines. An important aspect of the new guidelines is also the focus in widening the network of reporting of AEFIs. District Immunization Officers are now responsible for reaching out to the clinicians in tertiary care hospitals in public and private sector (including medical colleges) and conducting sensitization sessions for doctors to report AEFIs. DIOs need to collaborate with professional bodies like IAP, IMA and API for this purpose. All these changes have been included in the revised edition of the Operational Guidelines for Surveillance and Response of AEFI-2024.

While the sensitivity of the AEFI surveillance programme has improved over the years, I hope this guideline will further enhance the capacity and capability of our health workforce to respond to vaccine safety challenges by efficiently implementing their roles and responsibilities. I sincerely appreciate the hard work of all the experts who contributed to the development of these revised guidelines.

(Dr. Pawan Kumar)



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Abbreviations

AC	Additional Commissioner
ADR	Adverse Drug Reaction
AD	Auto-disable
AE	Adverse Events
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
AFP	Acute Flaccid Paralysis
AMC	ADR Monitoring Center
ANM	Auxiliary Nurse Midwife
aP	Acellular Pertussis
API	The Association of Physicians of India
ASHA	Accredited Social Health Activist
AWW	Anganwadi Worker
BA/ BE	Bioavailability & Bioequivalence
BCG	Bacillus Calmette-Guerin
BCPNN	Bayesian Confidence Propagation Neural Network
CA	Causality Assessment
CAS	Critical Appraisal Skills
CBHI	Central Bureau of Health Intelligence
CDL	Central Drugs Laboratory
CDSCO	Central Drug Standard Control Organization
CEPI	Coalition for Epidemic Preparedness Innovations
CGHS	Central Government Health Scheme
CHC	Community Health Center
CHRD SAS	Centre for Health Research and Development Society for Applied Studies
CIF	Case Investigation Form
CIOMS	Council for International Organizations of Medical Sciences
CLA	Central Licensing Authority
CMO / CS	Chief Medical Officer / Civil Surgeon
CNF	Case Notification Form
CNS	Central Nervous System
COVID-19	Coronavirus disease
Co-WIN	Covid Vaccine Intelligence Network
CRF	Case reporting form
CSF	Cerebrospinal fluid
CT	Clinical Trial
DAC	District AEFI Committee
DCG (I)	Drug Controller General of India

D & C act	Drugs and Cosmetics Act
DGHS	Director General of Health Services
DH	District Hospital
DI	Drug Inspector
DIO	District Immunization Officer
DMEIO	District Mass Education Information Officer
DNA	Deoxyribonucleic acid
DPT	Diphtheria–Pertussis (whole-cell)–Tetanus vaccine
DQAC	District Quality Assurance Committee
DSNR	Dissociative Neurological Symptoms Reaction
DTap	Diphtheria-tetanus-pertussis (acellular) vaccine
DTwP	Diphtheria-tetanus-pertussis (whole-cell) vaccine
ECG	Electro cardiogram
EPI	Expanded Programme on Immunization
ESI	Employees' State Insurance
EUA	Emergency Use Authorization
FLW	Front level workers
FMR	Financial Management Report
FNAC	Fine Needle Aspiration Cytology
FSL	Forensic Science Laboratory
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré Syndrome
GBT	Global Benchmarking Tool
GMP	Good Manufacturing Practice
GoI	Government of India
GVSI	Global Vaccine Safety Initiative
HBV/ Hep B	Hepatitis B Vaccine
HDCV	Human Diploid Cell Vaccine
HHE	Hypotonic Hypo-responsive episode
Hib	Haemophilus influenza type b vaccine
H1N1	Influenza A virus subtype
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigens
HMIS	Health Management Information system
HPV	Human Papillomavirus
HQ	Headquarters
HS	Health Supervisor
IAP	Indian Academy of Pediatrics
ICD 10	International Classification of Diseases 10th edition
ICDS	Integrated Child Development Services
ICMR	Indian Council of Medical Research

ICSR	Individual Case Safety Report
ID	Intradermal
IDSP	Integrated Disease Surveillance Program
IEC	Information Education Communication
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ILR	Ice Lined Refrigerator
IM	Intramuscular
IMA	Indian Medical Association
IMR	Infant Mortality Rate
INCLEN	International Clinical Epidemiology Network
IOM	Institute of Medicine
IP	Indian Pharmacopoeia
IPC	Indian Pharmacopoeia Commission
IPC	Interpersonal Communication
IPHA	Indian Public Health Association
IPRS	Indian Pharmacopoeia Reference Standards
IPV	Injectable polio vaccine
ISQua	International Society for Quality in healthcare
ISRR	Immunizaton Stress-Related Response
ITP	Immune Thrombocytopenic Purpura
ITSU	Immunization Technical Support Unit
ITSR	Immunization Triggered Stress Response
IV	Intravenous
JE	Japanese Encephalitis
LAV	Live attenuated vaccine
LHV	Lady Health Visitor
LRF	Laboratory Request form
MAASS	Multi-centre Active AEFI Sentinel Surveillance Network
MAH	Market Authorization Holder (manufacturer / Importer)
MCP	Mother and Child Protection Card
ME	Measurable Elements
MHC	Major Histocompatibility Complex
MLC	Medico Legal Case
MMR	Measles – mumps – rubella vaccine
MO I / C	Medical officer In-charge
MOHFW	Ministry of Health and Family Welfare
MPR	Monthly Progress Report
MR	Measles – rubella vaccine
NABL	National Accreditation Board for Testing and Calibration Laboratories
NAC	National AEFI Committee
NACO	National AIDS Control Organisation

NaF	Sodium Fluoride
NATCC	National AEFI Technical Collaborating Centre
NCC-PVPI	National Coordination Center for PVPI
NCDC	National Centre for Disease Control
NHM	National Health Mission
NHSRC	National Health Systems Resource Centre
NIV	National Institute of Virology
NQAS	National Quality Assurance Standard
NRA	National Regulatory Authority
NSQ	Not of Standard Quality
NTAGI	National Technical Advisory Group
OPD	Out Patient Department
OPV	Oral Polio vaccine
PCEV	Purified Chick Embryo Cell vaccine
PCV	Pneumococcal conjugate vaccine
PHC	Primary Health Center
PI	Prescribing Information
PIP	Program Implementation Plan
PMS	Post Marketing Surveillance
PRR	Proportional Reporting Ratio
PSU	Public Sector Undertaking
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
PVPI	Pharmacovigilance Program of India
PVRV	Purified Vero cell Rabies vaccine
PVV	Pentavalent (DTP-HepB-Hib) vaccine
QA	Quality Assurance
QMS	Quality Management System
RCH	Reproductive and Child Health
RI	Routine Immunization
RJ	Radio Jockey
RMP	Risk Minimization Plan
RMP	Registered Medical Practitioner
RNA	Ribonucleic acid
RNI	Registrar of Newspaper of India
ROR	Reporting Odds Ratio
SAC	State AEFI Committee
SAE	Serious Adverse Event
SAFE-VAC	Surveillance and Action for Events Following Vaccination
SAGE	Strategic Advisory Group of Experts on Immunization
SC	Sub Center
SC	Subcutaneous

SCCS	Self-Controlled Case Series
SDH	Sub-divisional Hospital
SDR	Signals of Disproportionate Reporting
SEC	Subject Expert Committee
SEPIO	State Immunization Officer / State EPI Officer
SIDS	Sudden Infant Death Syndrome
SmPC	Summary of Product Characteristics
SOPs	Standard operation procedures
SPEAC	Safety Platform for Emergency Vaccines
SQAC	State Quality Assurance Committee
SRP	Signal Review Panel
SSS	Smart Safety Surveillance
Td	Adult tetanus-diphtheria vaccine
THSTI	Translational Health Science and Technology Institute
TOR	Term of Reference
TNAI	Trained Nurses' Association of India
TSS	Toxic Shock Syndrome
TT	Tetanus Toxoid
TTS	Thrombotic Thrombocytopenia Syndrome
UHC	Urban Health Center
UIP	Universal Immunization Programme
UNDP	United Nations Development Programme
UNICEF	United National Children's Fund
USAID	United States Agency for International Development
UT	Union Territory
U-WIN	Universal Immunization Programme Vaccine Intelligence Network
VAERS	Vaccine Adverse Event Reporting System
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VPD	Vaccine Preventable Disease
VVM	Vaccine Vial Monitor
VZV	Varicella Zoster Virus
WHO	World Health Organization
WHO-NPSN	World Health Organization- National Public Health Support Network

1 Introduction

It is a well-established fact that vaccines protect against vaccine-preventable diseases (VPD), reducing the incidence and severity of diseases and saving lives. Vaccinations provided under the Universal Immunization Programme in India are voluntary. The goal of immunization is to protect the individual and the public from vaccine-preventable diseases by ensuring every individual receives all due vaccines at the appropriate age. Although vaccines are safe, no vaccine is entirely without risk, and adverse reactions will occasionally occur following immunization. It is also important to note that the benefits of vaccination far outweigh the risks related to or perceived to be due to vaccines.

Before a vaccine is approved for use in humans, it undergoes rigorous pre-clinical assessment followed by three phases of clinical trials. Following rigorous assessments of the clinical trial data, the vaccine may be licensed by the regulator (CDSCO in India) for use. Clinical trials, due to limited number of volunteers in which the vaccine is tested, may not be able to identify rare adverse events. A strong AEFI surveillance system monitors the safety of the vaccine in millions of beneficiaries to capture rare adverse events, analyse them and take appropriate actions to ensure vaccine safety.

Immunization safety covers the entire spectrum of vaccine safety and quality ranging from vaccine manufacturing, regulation, safe administration, waste disposal and AEFI surveillance. The AEFI surveillance system in India captures data on adverse events following any vaccination, and not just for UIP vaccines or paediatrics vaccines. Adverse events following other vaccines such as rabies vaccine, flu vaccines, vaccines given to populations living in specific geographies (such as Kyasanur Forest Disease vaccine) and vaccines recommended for international travel (such as yellow fever vaccine), or to specific age groups or gender such as HPV, etc. are also reported to the AEFI surveillance system.

The objectives of the AEFI surveillance system are (i) to promptly detect, report and respond to AEFI; (ii) expeditious identification of unusually high rates of AEFI related to a specific vaccine lot/brand; (iii) promptly address programmatic errors through implementation of corrective measures; (iv) estimate serious AEFI rates in the population and compare these with local and global data and; (v) identify signals of unexpected adverse events and generate new hypotheses about these events that must be confirmed by planned studies and laboratory investigations. Through the AEFI surveillance programme, the safety profile of the vaccines can be monitored to help regulators and programme managers take necessary actions and continuously conduct benefit-risk assessments to inform public health policies and sustain public confidence. Causality assessment of the adverse event helps distinguish a coincidental event from a true vaccine-related event. All healthcare providers should be aware of different aspects of AEFIs and be prepared to respond appropriately and timely to public concerns to

maintain trust in the immunization programme.

India, being a major vaccine manufacturer has a greater responsibility to ensure that critical control functions (including vaccine pharmacovigilance), are implemented in a competent and independent manner. It gives confidence to other countries that vaccines manufactured and used in India are safe.

The National AEFI Guidelines of 2005 were revised in 2010 and 2015. Since then, the WHO has assessed the AEFI surveillance system of the country as part of the periodic NRA assessment in 2017 and declared the country's AEFI surveillance system robust. The COVID-19 mass vaccination campaign was used as an opportunity to further strengthen the AEFI surveillance system. These guidelines provide the reader with technical and operational updates and details of the improvements made to the surveillance system since 2015. Some of the key changes made in the surveillance system are:

1. Use of digital vaccination recording software (SAFE-VAC, U-WIN) to increase reporting of all AEFIs, including minor ones; changes in HMIS reporting; reduction in the number of Case Investigation Forms (CIFs); timeline for submission of CIF increased to 21 days from 10 days. (Chapter 4)
2. Vaccinators allowed to administer one dose of adrenaline intramuscularly in a suspect case of anaphylaxis and dispensing of syrup paracetamol in place of tablet paracetamol at vaccination session sites for managing minor AEFIs (Chapter 3)
3. Updated post-mortem guidelines for AEFI death investigations in adults and children; new verbal autopsy form for adults. (Chapter 6)
4. Expansion of Quality Management System for AEFI surveillance to the states, districts, PHCs and session sites. (Chapter 12)
5. Inclusion of physicians, neurologists, cardiologists, respiratory medicine specialists and obstetrician-gynaecologists in AEFI committees; greater role of state AEFI committees and state AEFI technical collaborating centre in medical colleges in investigations, causality assessments, capacity-building and monitoring activities at the district level. (Chapter 9)
6. Strengthening the AEFI surveillance system for introduction of adult vaccinations and new vaccines in the UIP and introduction of new vaccines under Emergency Use Authorization as part of pandemic preparedness. (Chapter 15)
7. Use of signal management processes for vaccines. (Chapter 10)

What is new in these guidelines are:

1. Updated information on new vaccines (adenovector, DNA) and updated safety profiles of COVID-19 vaccines and other non-UIP and non-paediatric vaccines (Chapters 2 and 3).
2. Changes made in the AEFI surveillance in adults (recommendations to expand network for capturing AEFIs in adults, revised formats, safety profiles of vaccines used in adults) (Chapters 3, 4, 5 and 14).
3. Number of vaccine vials to be sent for testing to Central Drugs Laboratory (CDL), Kasauli for new vaccines. (Chapter 7).

4. Changes to the causality assessment process, checklist, summarizing reasons for classification, description of underlying mechanisms and limitations of causality classification of a case (Chapter 8).
5. Changes in the roles and responsibilities of District Immunization Officers, (for expanding reporting network to private and public sector hospitals), collaboration with Quality Assurance teams at state and district levels, updated monitoring indicators for AEFI surveillance (Chapter 9).
6. Updated data-sharing mechanisms between pharmacovigilance partners and drug regulators including processes for sharing of recommendations of safety signals for regulatory actions (Chapter 13).
7. Using social media to convey messages on the benefits of vaccination and responding to a crisis (Chapter 11).

These guidelines are intended for health workers and medical officers at various health facilities, programme managers at the PHC level, district and state level, members of the AEFI committees at all levels, partner agencies including drug regulators at all levels, state AEFI technical collaborating centres in medical colleges, faculties and students of medical colleges, and other stakeholders in the private and public sector involved in or responsible for vaccine safety and quality.

2 Principles of Immunization and Vaccines

2.1 Immunity

Immunity[1] is the ability of the human body to tolerate the presence of materials indigenous to the "body" (self) and to identify & eliminate "foreign" (non-self) materials. This discriminatory ability provides protection from infectious diseases, since most of the microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibodies against that organism. Immunity is generally very specific to a single organism or a group of closely-related organisms. There are two main types of immunity- innate and adaptive immunity.

2.1.1 Innate Immunity

Innate immunity is the body's first line of defense against pathogens. It is not specific to a particular pathogen and provides immediate protection against a broad range of potential invaders. It is carried out by various components of the body such as the skin, mucous membranes, complement proteins, natural killer cells, phagocytes (e.g., neutrophils and macrophages), and dendritic cells. These components work together to detect and destroy foreign invaders or antigenic exposure in a variety of ways, such as engulfing and digesting them, releasing toxic chemicals, and activating the adaptive immune response.

2.1.2 Adaptive Immunity

Adaptive immunity is the body's second line of defence, which is activated after the innate immune system has identified a specific pathogen or foreign antigen. This type of immunity involves the production of antibodies & the activation of immune cells called T cells and B cells, which work together to specifically target and eliminate the invading pathogen through several complicated mechanisms. Adaptive immunity is highly specific and has a memory, meaning that the body can recognize and respond more quickly to previously encountered pathogens and/or antigens. There are two main mechanisms of immunity within the adaptive immune system - humoral and cell-mediated.

Humoral immunity is also called antibody-mediated immunity. With assistance from helper T cells, B cells will differentiate into plasma B cells that can produce antibodies against a specific antigen. The humoral immune system deals with antigens from pathogens that are freely circulating, or outside the infected cells. Antibodies produced by the B cells will bind to antigens, neutralizing them, or causing lysis (dissolution or destruction of cells by a lysin) or phagocytosis.

1. *Global manual on surveillance of adverse events following immunization. WHO, 2014*

Cell mediated immunity occurs inside the infected cells and is mediated by T lymphocytes. The pathogen's antigens are expressed on the cell surface or on an antigen-presenting cell. Helper T cells release cytokines that help activated T cells bind to the infected cells' MHC-antigen (Major Histocompatibility Complex-antigen) complex and differentiate the T cell into a cytotoxic T cell. The infected cell then undergoes lysis.

There are two basic mechanisms for acquiring immunity: active and passive.

Active immunity is the stimulation of the host immune system to produce antigen-specific response. Usually, it lasts for many years, often for the lifetime. One way to acquire active immunity is to survive infection from the disease-causing organism or exposure to the antigen to which the body responds by forming memory cells. Upon re-exposure to the same antigen, these memory cells begin to replicate and produce antibodies very rapidly to re-establish protection.

Another way to produce active immunity is by vaccination. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but without subjecting the recipient to the disease & its potential complications. Effective immunizations must induce long-term stimulation of both the humoral and cell-mediated arms of the immune system by the production of effector cells for the current exposure and memory cells for future infections with the pathogenic agent.

Many factors may influence the immune response of the body to vaccination. These include the presence of maternal antibody or antibodies from prior natural infection, nature and dose of antigen, route of administration, and the presence of an adjuvant (e.g. aluminium containing material) added to improve the immunogenicity of the vaccine. Host factors such as age, nutritional factors, genetics and coexisting disease may also affect the response.

Passive immunity is the transfer of antibodies produced by one human or animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies degrade over time. The most common form of passive immunity is that which an infant receives from its mother. The antibodies received from the mother protect the infant from certain diseases for a variable period (usually from a few months to a year). The administration of specific antibodies against infective agents (e. g. anti-diphtheria toxin) also confers immediate albeit transient immunity.

2.1.3 Herd Immunity

Herd immunity (or community immunity) describes a type of immunity that occurs when the vaccination of a portion of the population (or herd) provides protection to the unprotected individuals in addition to the vaccinated individuals. Herd immunity theory proposes that the chain of infection breaks when large numbers of a population acquires immunity against the specific pathogen, specifically in diseases which are circulated from one individual to other. The

higher the number of immune individuals, the lower the likelihood that a susceptible person will come into contact with an individual harbouring the infectious agent. From both theoretical and practical perspectives, the disease usually disappears before immunization levels reach 100%, as has been seen with smallpox, poliomyelitis and measles. The proportion of immune individuals in a population, above which a disease may no longer persist, is the herd immunity threshold. The threshold value for herd immunity varies with the virulence of the disease, the efficacy of the vaccine, the population composition, and distribution of vaccinated /unvaccinated individuals across the population.

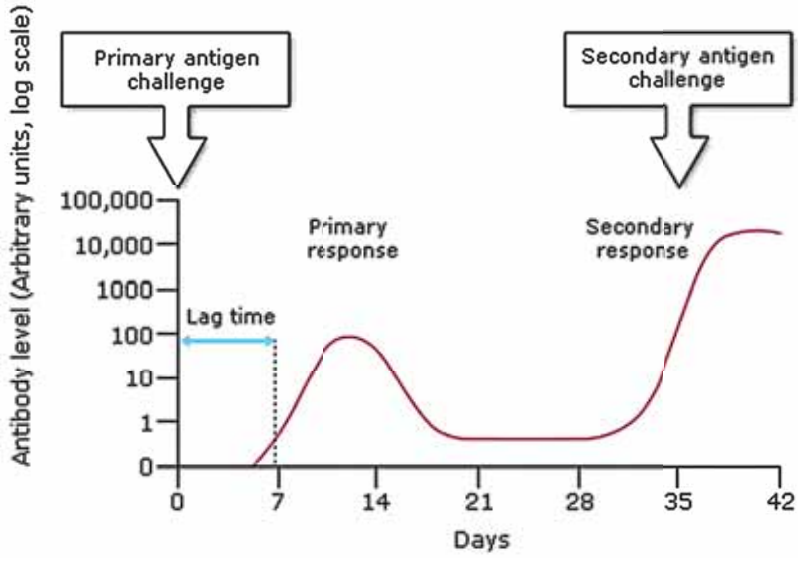
2.1.4 How Does Immunization Work?

There are many types of vaccines, but they all work on the same principle - by preparing the immune system to attack the infection. Basically, a vaccine contains components that are more or less similar to the infecting organism. So, the immune system responds as it would to an infection with that organism. The most important consequence of successful vaccination is that it produces long-lived memory lymphocytes that respond more quickly and in a more coordinated way to subsequent infections. As a result, the infectious organism is destroyed more quickly or the damaging effect is prevented. The protection with a vaccine is not always complete i.e. an infection may not always be prevented but the severity of the illness is usually reduced.

The first exposure to a vaccine stimulates the immune response of the body (also known as priming). The immune system takes time to respond to the antigen by producing antibodies and immune cells. Initially, immunoglobulin M (IgM) antibody is produced but this occurs in small amounts and does not bind very strongly to the antigen. After a few days, the immune response begins to make immunoglobulin G (IgG) antibody, which is more specific to the microbe and lasts longer than IgM (Figure 2.1).

Subsequent administration of the same vaccine stimulates the secondary response. The secondary response is much faster than the primary response and produces predominantly IgG antibodies rather than IgM. The aim is to generate enough immune cells and antibodies, specific to the infectious microbe, to provide long-lasting protection against the disease.

Figure 2.1: Primary and Secondary Response to an Antigen



The secondary response may be more effective, eliminating pathogens before any damage occurs.

2.2 Vaccine

A vaccine is a biological product that improves and enhances immunity to a given disease. A vaccine contains a disease-causing microorganism, or a portion of it, and is often made from either live-attenuated or inactivated (killed) forms of the microbe, its sub-component protein (toxin or one of its surface proteins), RNA or DNA.

Vaccines may be monovalent or multivalent. A monovalent vaccine contains a single strain of a single antigen (e.g. measles vaccine), whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen (e.g. oral poliovirus vaccine, HPV, influenza).

Combined vaccines contain two or more antigens (e.g. DTwP, DTP-HepB-Hib/pentavalent vaccine). Potential advantages of combination vaccines include reducing the cost of stocking, cold chain storage space improving compliance by reducing the number of pricks for administering separate vaccines, reducing the cost of extra health-care visits and, improving timeliness of vaccination, thereby facilitating the addition of new vaccines into immunization programmes.

There is no evidence that the administration of several antigens in combined vaccines increases the burden on the immune system, which is capable of responding to millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions and can, in fact, lead to an overall reduction in adverse reactions.

2.2.1 Classification of Vaccines

There are four broad types of vaccines used at present under the routine immunization program: live-attenuated, inactivated (killed antigen), subunit (purified antigen) and toxoids (inactivated toxic compounds). The characteristics of these types of vaccines are different, which determine how the vaccines work.

A. Live-Attenuated Vaccines (LAVs)

LAVs are derived from "wild," or disease-causing virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing under special conditions. The resulting vaccine organism retains the ability to replicate (grow) in the vaccinated person and produce immunity, but usually does not cause the illness. The immune response to a LAV is virtually identical to that produced by a natural infection. These LAV can cause disease in immunocompromised individuals and thus are contraindicated for these persons. In pregnancy, live attenuated vaccines are generally contraindicated as LAV poses a theoretical risk to the foetus.

For LAV, the first dose usually provides protection. An additional dose is given to ensure seroconversion in all recipients. For instance, 95% to 98% of recipients will respond to a single dose of measles vaccine. The second dose is given to assure that nearly 100% of recipients are immune (i.e., the second dose is "insurance"). Immunity following LAV is long-lasting, and booster doses are not necessary, with the exception of oral polio vaccine, which requires multiple doses.

The immune response to LAV is affected by presence of circulating antibodies (either vertically transferred or from prior infections). LAV are labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully. Currently available LAV target viruses (measles, mumps, rubella, varicella, yellow fever, oral polio, rotavirus, and influenza-intranasal) and bacteria (Bacille Calmette-Guérin (BCG) and oral typhoid vaccine).

B. Inactivated Whole-Cell Vaccines

Inactivated (or killed) vaccines are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formalin). Because they are not alive, they cannot grow in a vaccinated individual and, therefore, cannot cause the disease, even in an immunodeficient person. Inactivated vaccines are generally safer than LAV, with no risk of inducing the disease. Unlike live antigens, inactivated antigens are usually not affected by circulating antibodies. They are often more stable than the LAV.

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only "primes" the immune system. A protective immune response is developed after multiple subsequent doses. In contrast to the LAV, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral and little or no cellular immunity results. Antibody titres against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost", antibody titres. Currently available inactivated/ killed vaccines are Polio (Inactivated Polio Virus, IPV), Hepatitis A and Rabies Vaccine.

C. Subunit Vaccines

Instead of the whole organism, subunit vaccines include only the antigens that best stimulate the immune response. Because subunit vaccines contain only the essential antigens and not all the other components of the microbes, there is no risk of illness and the chances of adverse reactions are lower. The subunit vaccines can be produced in two ways:

1. The whole organism is grown in culture media and then the organism is further treated to purify only those components to be included in the vaccine (e.g. acellular pertussis and the meningococcal B vaccine).
2. Antigen molecules from the microbes can be manufactured using recombinant DNA technology. Vaccines produced in this way are called 'recombinant sub-unit vaccines'

Depending upon the type of antigens, the subunit vaccines are of three types:

C.1 Protein-Based Recombinant Vaccines

Subunit vaccines can be protein-based. For example, the hepatitis B vaccine is made by inserting a segment of the hepatitis B virus gene into a yeast cell. The modified yeast cell produces large amounts of hepatitis B surface antigen, which is purified and harvested to produce the vaccine. The recombinant hepatitis B vaccine is identical to the natural hepatitis B surface antigen, but does not contain virus DNA and is unable to produce infection. Another protein-based vaccine is acellular pertussis (aP) vaccine which contains inactivated pertussis toxin (protein).

C.2 Polysaccharide Vaccines

Many bacteria have a polysaccharide outer wall. In the polysaccharide vaccine, only the sugar part of the bacteria, the capsule, is included as the antigen to stimulate the immune response. Meningococcal and pneumococcal polysaccharide vaccines contain the polysaccharide capsules of the encapsulated bacteria which are purified and made non-infectious.

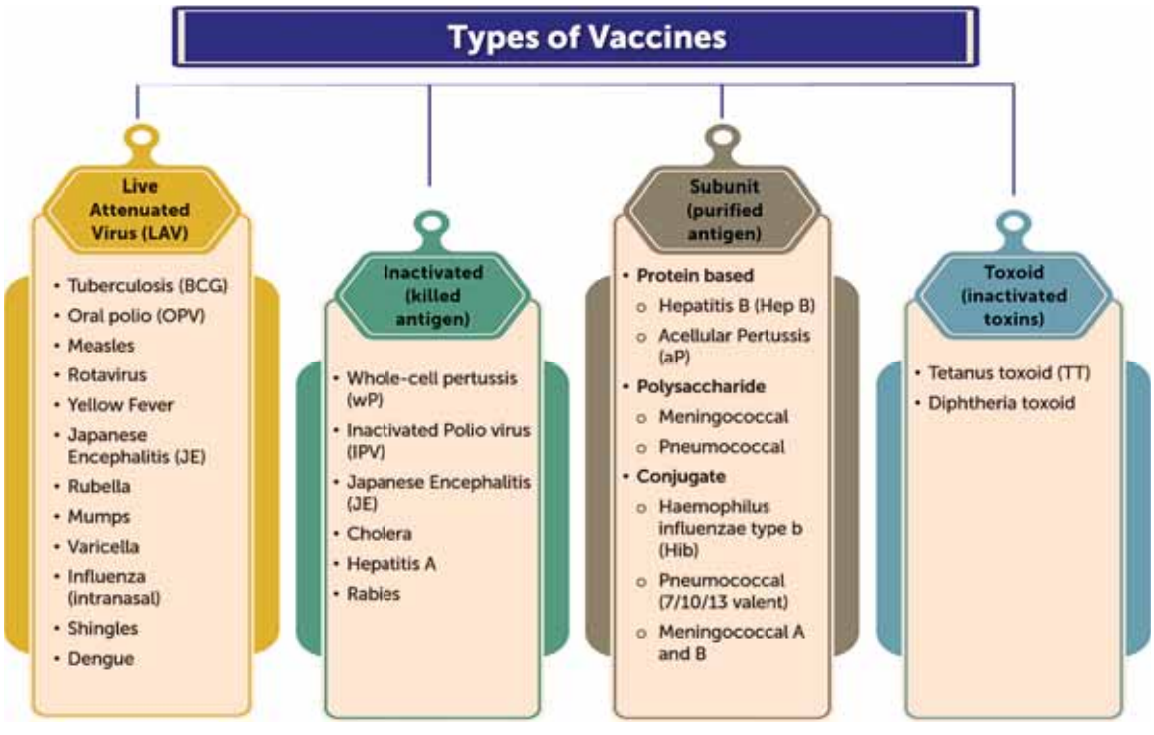
C.3 Conjugate Vaccines

The immature immune system of children under two years of age does not respond well to the polysaccharide antigens, which lead to antibody production via a T-cell independent mechanism. If these polysaccharide antigens are chemically linked (conjugated) to a protein that enables T-cell recognition, then these conjugate vaccines can elicit strong immune responses and immune memory in young children. The Haemophilus influenzae type b conjugate (Hib) and Pneumococcal conjugate vaccine (PCV) are the examples of conjugate vaccines.

D. Toxoid Vaccines

In some bacterial infections (e.g. diphtheria, tetanus), the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by purifying the toxin and altering it chemically (usually with formaldehyde). The toxoid, while no longer toxic, is still capable of inducing a specific immune response protective against the effects of the toxin. The various types of vaccines with examples are summarised in Figure 2.2 (also refer to **Annexure 1**).

Figure 2.2: Types of Vaccines



COVID-19 Vaccines

COVID-19 vaccines are intended to provide acquired immunity against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). In order to respond quickly and effectively to the COVID-19 pandemic, a broad range of COVID-19 vaccines (Table 2.1) were manufactured globally using various technologies and platforms. These include viral-vectored, protein subunit, nucleic acid (DNA, RNA), live attenuated and inactivated vaccines.

Table 2.1: List of COVID-19 Vaccines

Vaccine Platform	Brand Name (Manufacturer)	Description
Messenger Ribonucleic Acid (mRNA)	Comirnaty (Pfizer/ BioNtech)	mRNA vaccines provide the instructions to human cells to make part of the SARS-CoV-2 spike protein. The spike protein triggers the recipient's immune system to develop a protective response which defends against future exposure to SARS-CoV-2.
	Spikevax (Moderna) Gemcovac-19 (Gennova)	
Viral Vector Based	Vaxzevria (Astra Zeneca)	A modified virus (the viral vector), other than the virus causing COVID-19, is used to deliver the instructions to human cells to make part of the SARS-CoV-2 spike protein. The spike protein triggers the recipient's immune system to develop a protective response which defends against future exposure to SARS-CoV-2. Sputnik V was the first coronavirus vaccine to use a heterogeneous boosting approach based on two different vectors in two separate vaccine shots.
	Covishield (Serum Institute of India)	
	Jcovden (Janssen)	
	Sputnik V Sputnik Light	
	iNCOVACC (Bharat Biotech Intl. Ltd.)	
Inactivated Virus	Coronavac (Sinovac)	An inactivated vaccine consists of killed virus or particles that are recognized by the immune system to elicit an immune response.
	Sinopharm	
	Covaxin (Bharat Biotech Intl. Ltd.)	
Recombinant Spike Protein Nanoparticle	Novavax and Covovax (Serum Institute of India)	Subunit vaccines contain specific fragments of the SARS-CoV-2 spike protein, which have been carefully selected to produce combinations of these molecules likely to produce a strong and effective immune response.
	Corbevax (Biological E. Limited)	

DNA Vaccine	ZyCoV-D / Plasmid DNA vaccine (Zydus Cadila Lifesciences Limited)	Genetically engineered DNA which codes for the spike protein of SARS-CoV-2 is inserted into DNA of a bacterial plasmid. This plasmid, when injected into the body, enters the cell. The cells of the body then use the instructions in the DNA of the plasmid to make the spike protein of SARS-CoV-2. The immune system is expected to recognize this as a threat and develop antibodies in response.

2.2.2 Other Components in Vaccines (Excipients)

Adjuvants

Sometimes a substance is added to a vaccine to enhance the immune response by degree and/or duration, making it possible to reduce the amount of immunogen per dose or the total number of doses needed to achieve immunity. The commonly used adjuvants are aluminium salts (aluminium hydroxide, aluminium phosphate or potassium aluminium sulphate) which primarily enhance the immune response to proteins. Several newer adjuvants (liposomes, squalene emulsified with surfactants –AS03, etc) are being used for the new generation of vaccines. They have been shown to be safe over several decades of use. Rarely, they may cause injection site reactions, including subcutaneous nodules, sterile abscess, granulomatous inflammation or contact hypersensitivity.

Antibiotics

Antibiotics are used during the manufacturing phase of vaccines to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. For example, MMR vaccine and IPV each contains less than 25 micrograms of neomycin per dose (less than 0.000025g). Persons who are known to be allergic to neomycin should be closely observed after vaccination so that any allergic reaction can be treated immediately.

Preservatives

These are chemicals (e.g. thiomersal, formaldehyde) added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and to prevent serious secondary infections as a result of bacterial or fungal contamination.

Stabilizers

To ensure product quality or stability, compounds may be added to vaccines for a variety of manufacturing-related issues: controlling acidity (pH); stabilizing antigens through necessary steps in the manufacturing process, such as freeze drying; and preventing antigens from adhering to the sides of glass vials with a resultant loss in immunogenicity. Examples of such additives include potassium or sodium salts, lactose, human serum albumin and a variety of animal proteins, such as gelatin and bovine serum albumin.

Trace elements

Vaccines may contain residual trace elements that are used for inactivating the organism like formaldehyde and residual cell culture materials.

Excipients are added to vaccines for different purposes and some of them are removed in subsequent manufacturing steps. However, minute "trace" amounts may remain in the final product. The amount present is only of consequence for individuals who are allergic to them.

2.3 Contraindications and Precautions

A contraindication to vaccination is a rare condition in a recipient which increases the risk of occurrence of a serious adverse reaction or a disease in the recipient due to host factors. Ignoring contraindications can lead to avoidable vaccine reactions. Most contraindications are temporary, and the vaccine can be administered later. Children with moderate or severe acute illness should not be administered vaccines until their condition improves. A serious (life-threathening) vaccine reaction is anaphylaxis. The other risk is occurrence of infection due to the live vaccine (bacteria or virus) in immunocompromised individuals.

The following are the general contraindications for vaccination[2]:

1. If child has documentation or history of anaphylaxis (serious allergic reaction) or other severe reaction to previous dose of vaccine or vaccine component.
2. Live vaccines should not be given to immunodeficient children and pregnant women. For example, do not vaccinate HIV infected children with measles containing vaccine while they are still immunodeficient.

In pregnancy, live attenuated vaccines are generally contraindicated as LAV poses a theoretical risk to the foetus.

For details of contraindications for each vaccine, refer to the product insert given by the manufacturer with the vaccine.

Precautions are not contraindications, but are events or conditions to be considered while determining if the benefits of the vaccine outweigh the risks (especially if the would-be recipient is an immunocompromised or pregnant person). However, sometimes precautions stated in the product inserts or labels can be inappropriately used as absolute contraindications, resulting in missed opportunities to vaccinate.

2. *Immunization Handbook for Health workers. MOHFW 2018*

Summary

- Immunity refers to the body's ability to defend itself against pathogens, including bacteria, viruses, fungi, and parasites.
- Immunity can be innate, meaning that it is present from birth and does not require prior exposure to a specific pathogen, or adaptive, meaning that it develops over time as a result of exposure to a specific pathogen.
- B cells and T cells are key components of the adaptive immune system, and work together to produce antibodies, destroy infected cells, and coordinate the immune response.
- Active immunity is the result of the body's own immune response to a pathogen or antigen. This can either occur naturally when a person is exposed to a disease-causing pathogen or can be acquired through vaccination, which involves the introduction of a small dose of harmless attenuated pathogen or its component to stimulate the development of a targeted immune response.
- Passive immunity is the result of receiving antibodies or other immune components from an external source. This can occur naturally, such as when a baby receives antibodies from their mother through the placenta or breast milk, or it can be acquired through medical interventions such as the administration of immunoglobulins.
- Vaccines are important in protecting the individuals against infectious diseases, and are designed to stimulate the immune system to recognize and defend against specific pathogens and are generally given before exposure to the pathogens.
- Vaccines can be made using a variety of different methods, including using weakened or inactivated pathogens, proteins or subunits of the pathogen, or genetic material (such as mRNA).
- Vaccines contain active immunogens as well as excipients (adjuvants, antibiotics, preservatives, stabilizers and trace elements). The vaccine recipient's body may react to any of these immunogens and excipients.
- A documented/known history of anaphylaxis to a previous dose of vaccine or vaccine component is a contraindication for vaccination.
- Live vaccines should not be given to immunodeficient children.
- Live vaccines are generally contraindicated in pregnancy.
- Precautions are not contraindications, but are events or conditions to be considered while determining if the benefits of vaccination outweigh the risks.
- Immunization programs can help to achieve herd immunity, which occurs when a large portion of a population is immune to a disease, making it less likely that the disease will spread.

3 Adverse Events Following Immunization - Basics

Vaccines used in national immunization programmes and licensed for use are extremely safe and effective. Nevertheless, like any biological product, no vaccine is perfectly safe and adverse reactions may occur. In addition to the vaccines themselves, the process of immunization is a potential source of an adverse reaction.

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 unfavourable or unintended disease, symptom, sign or abnormal laboratory finding.

Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. A vaccine reaction is an individual's response to the inherent properties of the vaccine, and may occur even when the vaccine has been prepared, handled and administered correctly. Any medical event which is adverse in nature and the onset of which has occurred following vaccination may be reported as an AEFI irrespective of whether this is a true AEFI or not.

3.1 Types of AEFI

Based specifically on the severity, cause and frequency, vaccine reactions or AEFIs may be broadly grouped as under:

(i) AEFIs by severity of the event:

(a) Minor reactions (common)

(a) Serious and Severe vaccine reactions (rare)

(ii) Cause-specific AEFIs:

(a) Vaccine product-related reactions

(a) Vaccine quality defect-related reactions

(a) Immunization error-related reactions

(a) Immunization-triggered stress response (ITSR)

Some AEFIs occur more frequently than others. Minor adverse events occur more commonly after vaccination as against severe/serious AEFIs which rarely occur. It is important to know the frequency of various adverse events. Categorization of vaccine reactions by frequency of occurrence is given in Table 3.1.

Table 3.1: Categorization of Adverse Events by Frequency of Occurrence

Frequency Category	Frequency in Rate	Frequency in %
Very Common	≥ 1/10	≥ 10%
Common (Frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (Infrequent)	≥ 1/1,000 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%

3.2 AEFI by Severity of Event

3.2.1 Common, Minor Vaccine Reactions

Most vaccine reactions are minor and self-limiting. The purpose of a vaccine is to induce immunity by causing the recipient's immune system to react to the vaccine. Local reaction, fever and systemic symptoms can result as a part of the immune response. In addition, some of the vaccine's components (e.g. adjuvant, stabilizers or preservatives) can lead to reactions. An effective and safe vaccine produces the best possible immunity and reduces these reactions to a minimum. The standard case definitions of AEFI have been provided by Brighton Collaboration (**Annexure 2**). The frequency of non-serious reactions likely to be observed with the commonly used vaccines are listed in Table 3.2 and Table 3.3.

Table 3.2: Frequency and Nature of Non-Serious AEs - UIP Vaccines

Vaccine	Local Reactions	Systemic Reactions	
	Pain, Swelling, Redness	Fever > 38°C	Irritability, Malaise and Systemic Symptoms
BCG	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%
Pertussis (DTwP/Penta)	up to 50%	up to 50%	up to 55%
Pnemucoccal (PCV) conjugate	~ 20%	~ 20%	~ 20%
IPV	~ 30%	-	–
Tetanus/DT/DTaP/Td	~ 10%	~ 10%	~ 25
JE (live attenuated)	5 – 7%	-	1%

Table 3.3: Frequency and Nature of Non-Serious AEs - COVID-19 Vaccines

Vaccine	Local Reactions	Systemic Reactions
Covishield	**Very Common**: Injection site tenderness, pain, warmth, pruritus, bruising **Common:** Injection site swelling, erythema, induration[3]	**Very Common:** Headache, nausea, myalgia, arthralgia, fatigue, malaise, feverishness, chills **Common:** Pyrexia, influenza-like illness, asthenia, pain in extremities, vomiting, diarrhoea **Uncommon:** Muscle spasms, abdominal pain, hyperhidrosis, pruritus, rash, urticaria, tinnitus, dizziness, somnolence, lethargy, paraesthesia, hypoaesthesia, decreased appetite, lymphadenopathy
Covaxin[4]	**Common:** Injection site pain **Uncommon:** injection site - pruritus, erythema, induration, swelling, tenderness	**Common:** Pyrexia, fatigue, myalgia, headache **Uncommon:** Nausea, diarrhoea, vomiting, abdominal discomfort, abdominal pain, chills, arthralgia, dizziness, oropharyngeal pain, pruritus, ocular hyperaemia, eye pain, asthenia, pain in extremity, musculoskeletal stiffness
Corbevax[5]	**Very common:** Injection site pain **Common:** Injection site erythema, pruritus, swelling **Uncommon:** Injection site warmth and rash **Rare:** Injection site irritation	**Very Common:** Myalgia **Common:** Headache, fatigue, pyrexia, chills, headache, arthralgia, nausea **Uncommon:** Pain, upper abdominal pain, diarrhoea, vomiting, urticaria, pain in extremity, dyspnea, somnolence
Sputnik V Light[6]	**Very Common:** Increased injection site temperature	**Very Common:** Hyperthermia, injection site tenderness, oedema, pruritus, asthenia, pain, malaise, pyrexia, decreased appetite **Common:** Nasal congestion, sore throat, rhinorrhoea, headache, asthenia, nausea, vomiting, dyspepsia **Rare:** Dizziness, syncope

3. *Summary of Product Characteristics for Covishield version 2.0, Marketing Authorisation Holder: Serum Institute of India Private Limited, updated on 21 February 2023. Accessed on 07 June 2023 -https://cdsco.gov.in/*
4. *Summary of Product Characteristics for Covaxin, Marketing Authorisation Holder: Bharat Biotech International Limited, updated in May 2022. Accessed on 07 June 2023 from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=ODgxOQ==*
5. *Summary of Product Characteristics for Corbevax version Version 3.3, Marketing Authorisation Holder: Biological E. Limited, updated in May 2022. Accessed on 07 June 2023 from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=ODgxOA==*
6. *Summary of Product Characteristics for Sputnik Light, Marketing Authorisation Holder: Dr. Reddy's Laboratories Limited, updated on 30 March 2022. Accessed on 07 June 2023 from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=ODgyMQ==*

Covovax[7]	**Very common:** Injection site pain **Common:** Injection site tenderness, erythema, swelling, induration	**Very common:** Pyrexia **Common:** Myalgia, arthralgia, nausea, fatigue, pain, malaise, headache
iNCOVACC[8] **(Intranasal)**	**Common:** Running nose, sneezing, nasal congestion, nasal pain, sore throat, lacrimation	**Common:** Fever, headache, myalgia, fatigue, nausea and vomiting

Frequency - Very common ≥10%; Common ≥1% and <1; Uncommon ≥ 0.1% and <1%; Rare ≥0.01% and <0.1%

The occurrence of local reactions such as pain, swelling and/or redness at the injection site varies by the type of antigen. For example, local reactions are very commonly (>10%) reported following the use of whole-cell DTP, whereas these occur at lower frequencies of 1-10% in acellular DTP. BCG causes a specific local reaction that starts as a papule (lump) two or more weeks after immunization, which becomes ulcerated and heals after several months, leaving a scar. This is a normal response to BCG vaccine and not an adverse event. Keloid (thickened scar tissue) from the BCG lesion is more common among Asian and African populations.

The occurrence of systemic reactions also varies by the type of antigen. Fever is a very common (>10%) systemic reaction reported for most antigens. Other common systemic reactions (e.g. irritability, malaise, loss of appetite) can also occur after many antigens. DTwP has more reports of these systemic reactions than DTaP. For Live Attenuated Vaccines (LAV) such as measles/MMR and OPV, the systemic reactions arise from vaccine virus infection. Measles vaccine causes fever, rash and/or conjunctivitis, but it is very mild compared to "wild" measles. However, for severely immunocompromised individuals, it can be severe, even fatal. Systemic reactions to OPV include diarrhoea, headache and/or muscle pain. These are uncommon and affect less than 1% of vaccinees.

It is important to note that these observed rates are expected as vaccine reactions or response to vaccine antigen. In fact, the incidence of their reporting provides an indirect clue to sensitivity of the AEFI surveillance system. However, if these reactions are reported at a rate significantly higher than expected for a vaccine, an investigation is needed to exclude vaccine quality defect or a programme error.

7. *Summary of Product Characteristics for Covovax, Marketing Authorisation Holder: Serum Institute of India Pvt. Limited, updated in June 2022. Accessed on 07 June 2023, accessed from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=ODgyNA==*
8. *Summary of Product Characteristics for iNCOVACC, Marketing Authorisation Holder: Bharat Biotech International Limited, updated in September 2022. Accessed on 07 June 2023 from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=OTAwOQ==*

3.2.2 Serious and Severe Vaccine Reactions

The terms 'serious' and 'severe' are often used as interchangeable terms, but they are not.

Severe Reactions

"Severe" reaction is a broader term, not used for regulatory purposes and includes the reactions that are higher in severity than minor reactions but does not necessarily lead to hospitalisation. Severe reactions may be disabling, but usually do not result in long-term problems. The event itself, however, may be of relatively minor medical significance. For example, fever is a common and relatively minor medical event, but according to severity, it can be described as low-grade or high-grade fever. Anaphylaxis is always a serious event and life-threatening, even if managed as an out-patient with quick recovery. Most of the rare vaccine reactions (e.g. seizures, thrombocytopenia, HHEs, persistent inconsolable screaming) do not lead to long- term problems. These may fall in the category of "severe" if managed at out-patient level. All "serious" reactions are "severe", while vice versa is not true.

SERIOUS AEFI

- Death
- Hospitalization
- Clusters
- Disability
- Congenital anomaly/ birth defect
- Media reports/ community or parental concern

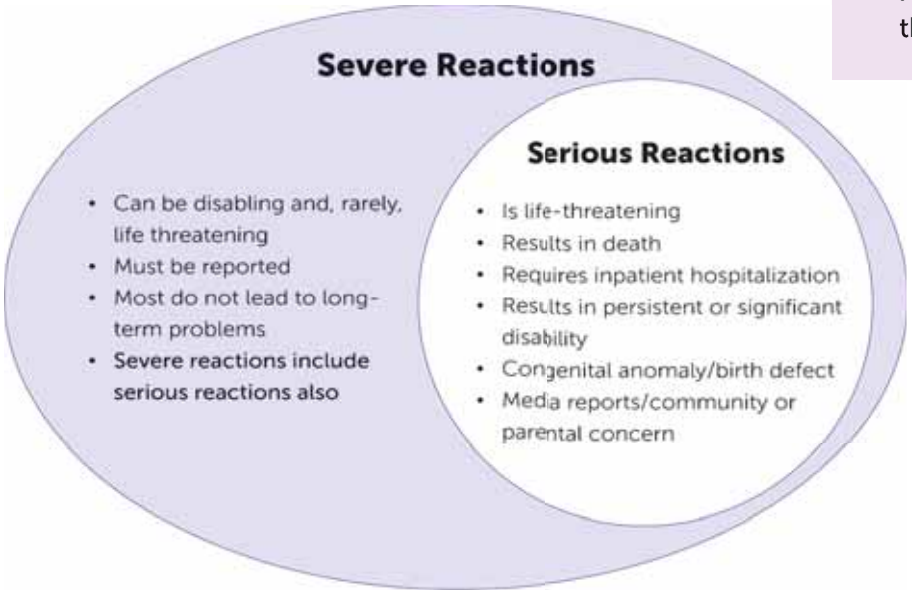
Serious Reactions

An AEFI will be considered 'serious', if it meets any of the following criteria: results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly/birth defect, requires intervention to prevent permanent impairment or damage. The term "serious" adverse event is used for regulatory purposes.

SEVERE AEFI

- Can be disabling and, rarely, life threatening
- Most do not lead to long-term problems
- Must also be reported
- Examples: seizures, hypotonic hypo responsive episodes (HHE), prolonged crying, thrombocytopenia

Figure 3.1: Serious and Severe Vaccine Reactions



The frequency and nature of severe & serious adverse events of commonly used vaccines are listed in Table 3.4.

Table 3.4: Frequency and Nature of Severe/Serious Adverse Events

Vaccines	Reaction	Time-to-Onset of Event	Frequency per Doses given
BCG [9, 10]	**Local:** Local Abscess, Keloid, Cutaneous skin lesions, Lymphadenitis, Suppuration	Onset 1-6 months	1 per 1,000-10,000 doses
	Systemic: Osteitis, Osteomyelitis, Disseminated BCG disease, Immune Reconstitution Syndrome (HIV patients)	Onset 1-12 months	1 per 80000 doses 1.5-4.29 per 1,000,000 doses 1 per 640,000 doses
OPV [11]	Vaccine Associated Paralytic Poliomyelitis (VAPP)	4 – 30 days	1 per 6,400,000 doses
DTwP/ Pentavalent (DTwP+HiB+HBV) [12, 13, 14]	**Mild adverse events:** Fever >38°C and irritability Drowsiness	0– 24 hours	40-75% 33-62%
	Prolonged inconsolable crying (>1 hr.) High fever >40.5°C	0– 24 hours	3.5% 0.3%
	HHE	0 – 48 hours	1-291 per 100,000 doses
	Seizure	0 – 72 hours	8-60 per 100,000 doses
	Acute Encephalopathy/ Encephalitis	2-11 days	1 per 310,000 to 5,300,000 doses
	Anaphylaxis/Shock	0 – 1 hour (may be upto 24 hours)	1-2 per 1,000,000 doses

9. *Brewer TF. Preventing Tuberculosis with Bacillus Calmette-Guérin Vaccine: A Meta-Analysis of the Literature [Internet]. Vol. 31, The Journal of the American Medical As-sociation. 1994. Available from: https://academic.oup.com/cid/article/31/Supplement_3/S64/331049*
10. *Information sheet on observed rate of vaccine reactions BCG vaccine. [Internet]. [cited 2023 Jun 14]. Available from: https://cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/bcg-vaccine-rates-information-sheet.pdf*
11. *Information sheet observed rate of vaccine reactions Polio vaccines. WHO, May 2014. [Internet]. [cited 2023 Jun 14]. Available from: https://www.who.int/publications/m/item/polio-vaccine-rates-information-sheet*
12. *WHO. Global Manual on Surveillance of Adverse Events Following Immunization. World Health Organization. 2021;2013–5.*
13. *Tam J, Tran D, Bettinger JA, Moore D, Sauvé L, Jadavji T, et al. Review of pediatric encephalitis and encephalopathy cases following immunization reported to the Canadian Immunization Monitoring Program Active (IMPACT) from 1992 to 2012. Vaccine [Internet]. 2020 Jun 9 [cited 2023 Jun 14];38(28):4457–63. Available from: https://pubmed.ncbi.nlm.nih.gov/32414652/*
14. *Information sheet observed rate of vaccine reactions DPT vaccines. WHO, May 2014. [Internet]. [cited 2023 Jun 14]. Available from: https://www.who.int/publications/m/item/DTP-vaccine-rates-information-sheet*

DTaP/ DTaP+Hib+HBV [14]	**Mild adverse events:** Fever >38°C and irritability, Drowsiness	0– 24 hours	20.3% 42.7%
	Prolonged inconsolable crying (>1 hr) High fever >40.5°C	0 – 24 hours	0-0.2% 0.9%
	Hypotonic hyporesponsive episodes	0 – 24 hours	14-62 per 100,000 doses
	Seizures	0 – 24 hours	0.5 per 100,000 doses
	Anaphylaxis	0 – 1 hour (may be upto 24 hours)	1 per 1,000,000 doses
Hepatitis B [15]	Anaphylaxis	0 – 1 hour (may be upto 24 hours)	1.1 per 1,000,000 doses
Measles/MR [16]	Fever >39.4°C Rash	7-12 days 7-10 days	5-15% 2-5%
	Febrile seizure	6-11 days	1 in 2000-3,000 doses
	Thrombocytopenia[17]	12-25 days (range 1-83 days)	1-40 per 1,000,000 doses
	Anaphylaxis	0-1 hour	1-3.5 per 1,000,000 doses
	Encephalopathy/ Encephalitis/ Encephalomyelitis	8-9 days	1 per 1,000,000 doses
Rubella[16]	Arthralgia/Arthritis/ Arthropathy	1-3 weeks	10-25% (mostly in adults)
Mumps[16]	Aseptic meningitis	2-3 weeks	13-900 per 1,000,000 doses
MMR vaccine[16]	Febrile seizure	5-12 days	40 per 100,000 doses

15. *Information sheet observed rate of vaccine reactions Hepatitis B vaccine. WHO, June 2012. WHO. 2012.*
16. *Information sheet observed rate of vaccine reactions MMR vaccines. WHO, May 2014. WHO. 2014.*
17. *Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. J Pediatr [Internet]. 2010 Apr [cited 2023 Jun 14];156(4):623–8. Available from: https://pubmed.ncbi.nlm.nih.gov/20097358/*

Tetanus/ Td[18]	Brachial Neuritis	0 – 60 days	0.69 per 10,000,000 doses
	Anaphylaxis	0 – 1 hour	1.6 per 1,000,000 doses
Rotavirus[19]	Intussusception	1- 7 days	1-6 per 100,000 first doses
Japanese Encephalitis (SA14-14-2, live attenuated) [20]	Serious Allergic Reactions	0 – 2 weeks	10 – 1000 per 1,000,000 doses
Japanese Encephalitis (Inactivated) [20]	Serious Allergic Reactions	0 – 2 weeks	10 – 1000 per 1,000,000 doses
	Seizures[21], Encephalopathy, Neuropathy, Myelitis, Aseptic Meningitis	0-2 days 3-42 days	1 per 1,000,000 doses (pooled)
Influenza (Inactivated) [22]	Anaphylaxis Guillain-Barré syndrome Oculo-Respiratory Syndrome	0-1 hour 2-7 weeks 2-24 hours	0.7 per 1,000,000 doses 1 – 2 per 1,000,000 doses 76 per 1,000,000 doses
Influenza (Live attenuated [22]	Anaphylaxis Wheeze Guillain-Barré Syndrome[23]	0-1 hour 0-42 days 2-7 weeks	2 per 1,000,000 doses
Varicella Zoster[24]	Febrile seizures	7-10 days	4 per 10,000 doses
HPV[25]	Myalgia, Arthralgia Anaphylaxis	0-1 hour	1-28 per 100 doses 1.7 per 1,000,000 doses

18. *Information sheet observed rate of vaccine reactions DPT vaccines. WHO, May 2014. WHO. 2014.*
19. *Information sheet observed rate of vaccine reactions Rotavirus vaccines. WHO, April 2014. WHO. 2014.*
20. *Information sheet observed rate of vaccine reactions JE vaccines. WHO, April 2014. WHO. 2014.*
21. *Plesner AM, Arlien-Søborg P, Herning M. Neurological complications to vaccination against Japanese encephalitis. Eur J Neurol [Internet]. 1998 Sep 1 [cited 2023 Jun 14];5(5):479–85. Available from: https://onlinelibrary.wiley.com/doi/full/10.1046/j.1468-1331.1998.550479.x*
22. *Information sheet on observed rate of vaccine reactions Influenza vaccines. WHO, July 2012. WHO. 2012.*
23. *Stratton K, Ford A, Rusch E, Clayton EW. Adverse Effects of Vaccines: Evidence and Causality. Adverse Effects of Vaccines: Evidence and Causality [Internet]. 2011 Apr 26 [cited 2023 Jun 14];1–894. Available from: https://pubmed.ncbi.nlm.nih.gov/24624471/*
24. *Information sheet observed rate of vaccine reactions Varicella zoster vaccine. WHO, July 2012. WHO. 2012.*
25. *Information sheet observed rate of vaccine reactions HPV vaccine. WHO, Dec 2017. WHO. 2017.*

Rabies[26]	**Local reactions:** Pain, Redness, Swelling induration	0-3 days	HDCV: 21-74% PCECV: 4% PVRV: 7%
	Systemic reactions: Fever, Headache, Dizziness, Gastrointestinal symptoms	0-5 days	HDCV: 7-55.6% PCERV: 15% PVRV: 6%
	Anaphylaxis	0-1 day	1 per 1,000,000 doses
	Guillain-Barré Syndrome[27]	12-85 days	<1 per 1,000,000 doses
Yellow fever [28]	Headache, Myalgia, Malaise, Fever Injection site pain, Swelling	1-10 days	15-31.4% 19.9-39.4%
	Viscerotropic disease	2-5 days	0.25-7.9 per 100,000 doses
	Neurotropic diseases (Encephalitis, Meningitis, Guillain-Barré Syndrome)	4-30 days	1-8 per 100,000 doses
Typhoid [29]	**Oral** Gastrointestinal, Fever **Injectable** Injection site pain, Erythema, induration, Headache **Serious reactions** - not reported	0-5 days 0-5 days	1.2-3.9% Up to 80% 3-7%
COVID-19 vaccines[30]	Anaphylaxis	0 – 1 hour (may be up to 24 hours)	5 per 1,000,000 doses administered

26. *Information sheet observed rate of vaccine reactions Rabies vaccine. WHO, June 2012. WHO. 2012.*
27. *Moro PL, Woo EJ, Paul W, Lewis P, Petersen BW, Cano M. Post-Marketing Surveillance of Human Rabies Diploid Cell Vaccine (Imovax) in the Vaccine Adverse Event Reporting System (VAERS) in the United States, 1990–2015. PLoS Negl Trop Dis [Internet]. 2016 Jul 13 [cited 2023 Jun 14];10(7). Available from: https://pubmed.ncbi.nlm.nih.gov/27410239/*
28. *Porudominsky R, Gotuzzo EH. Yellow fever vaccine and risk of developing serious adverse events: a systematic review. Revista Panamericana de Salud Pública [Internet]. 2018 [cited 2023 Jun 14];42. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6386100/?report=printable*
29. *Information sheet observed rate of vaccine reactions Typhoid vaccine. WHO, April 2014. WHO. 2014.*
30. *Overview of anaphylaxis and allergic reactions following COVID-19 immunisation [cited 2023 Jun 15]; Available from: https://www.lareb.nl/media/3e1lkfix/signals_2022_overview-of-anaphylaxis-and-allergic-reactions_covid19-vaccines.pdf*

Covishield [31, 32]	Thrombotic Thrombocytopenia Syndrome (TTS)	3- 30 days	0.5 to 6.8 cases per 100 000 doses administered
	Thrombocytopenia	10 days (1-78 days)	8 per 1,000,000 doses administered

3.3 Cause-Specific AEFIs

In 2018, the Council for International Organizations of Medical Sciences (CIOMS) and WHO revised the existing classification relevant to cause-specific categorization of AEFIs (Table 3.5).

Table 3.5: Cause-Specific Categorization of AEFI

Cause-specific AEFI	Definition
Vaccine product-related reaction	An event that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An event 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.
Immunization error-related reaction (formerly "programme error")	An event that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization triggered stress response (earlier Immunization anxiety-related reaction)	An event arising from anxiety about the immunization.
Coincidental event	An event that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Reference: CIOMS/WHO 2018 Note: "Immunization" as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. handling, prescribing and administration of the vaccine.	

The cause-specific categorization is important for decision-making on safety of a vaccine product.

31. *Guidance for clinical case management of TTS following vaccination to prevent COVID-19 [Internet]. [cited 2023 Jun 15]. Available from: https://www.who.int/publications/i/item/9789240061989*
32. *Gordon SF, Clothier HJ, Morgan H, Buttery JP, Phuong LK, Monagle P, et al. Immune thrombocytopenia following immunisation with Vaxzevria ChadOx1-S (AstraZeneca) vaccine, Victoria, Australia. Vaccine. 2021 Nov 26;39(48):7052–7.*

3.3.1 Vaccine Product Related Reaction

Vaccine product-related reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. This may be due to immune-mediated reaction of the individual or replication of vaccine-associated microbial agent (e.g. attenuated live virus or bacteria). Immune-mediated reactions are in general mild. However, it is important to note that among certain high-risk individuals there is a tendency of triggering adverse reactions, which would not occur in the majority of vaccinees. For example, fever is a common minor reaction following vaccination, but it can trigger seizures among children with an underlying seizure disorder or those with a propensity for febrile seizures. Other examples of vaccine product related reactions are anaphylaxis and allergic reactions.

3.3.2 Vaccine Quality Defect Related Reaction

Vaccine quality defect-related reaction is a defect in a vaccine that occurred during the manufacturing process. Such a defect may have an impact on an individual's response and thus increase the risk of adverse vaccine reactions. Insufficient inactivation of wild type vaccine agent (e.g. wild polio virus) during the manufacturing process or a contaminant introduced during manufacturing process could cause the vaccine quality defect-related reactions. In early years of immunization programmes, a few major incidences of vaccine quality defect-related reactions were reported. However, with introduction of Good Manufacturing Practices (GMP) and strengthening of national regulatory authorities, the potential risks of such quality defects are now very low and extremely rare.

Case Study: Vaccine Quality Defect Related Reaction	In 1955, after administration of the polio vaccine manufactured by Cutter laboratory in the US, 40,000 people developed abortive polio; 200 were permanently paralyzed and 10 died. Investigations revealed that two production pools of 12,000 doses contained live virus. It was identified that the process of inactivation of live virus was defective. ***Cause:*** Vaccine quality defect-related reaction http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/

3.3.3 Immunization Error–Related Reactions

The term "Immunization error related reactions" refers to errors related to all processes that occur after a vaccine product has left the manufacturing/ packaging site, i.e. prescribing, preparation, handling, storage and administration of the vaccine. This type of AEFI was earlier categorized as "programme error".

Immunization error related reactions are preventable and they affect the trust in immunization programmes (Table 3.6). The identification and correction of these errors in a timely manner are, therefore, of great importance.

Table 3.6: Types of Immunization Errors & Related Reactions

Immunization Error		Related Reaction
Error in vaccine prescribing or non-adherence to recommendations for use of the vaccine	• Failure to adhere to a contraindication • Failure to adhere to vaccine indication, dose or schedule.	• Disseminated infection with an attenuated live vaccine in an immune-compromised individual • Anaphylaxis in an individual with known allergy • Systemic and/or local reactions
Non-sterile injection administration	• Reuse of disposable syringe or needle leading to contamination of the vial, especially in multi-dose vials • Improperly sterilized syringe or needle • Contaminated vaccine or diluent • Reuse of reconstituted vaccine in subsequent sessions	• Local injection site reactions (e.g., abscess, cellulitis) • Sepsis, toxic shock syndrome • Blood-borne transmission of disease, e.g., hepatitis B or C, HIV, • Death
Error in vaccine reconstitution or use of vaccine with abnormal physical condition	• Reconstitution with incorrect diluent (drug substituted for vaccine or diluent) • Using vaccine with changed colour, turbidity, presence of foreign substances • Inadequate shaking of vaccine • Improper syringe filling	• Effect of wrong diluent (e.g., insulin, oxytocin, muscle relaxants) • Death • Local abscess • Increased local reaction (induration, pain) • Loss of vaccine potency
Error in vaccine handling	• Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents where applicable) • Not maintaining cold chain at the session site or use beyond recommended time after reconstitution • Freezing of vaccine during transport • Use of a product after the expiry date	• Systemic or local reactions due to changes in the physical nature of the vaccine such as agglutination of aluminium-based excipients in freeze-sensitive vaccines. • Toxic shock syndrome • Loss of vaccine potency
Error in administration	• Incorrect technique/site of injection (BCG / DPT/dT/TT given subcutaneously, injection into buttocks in infants or medially on thighs or use of wrong needle)	• Local reaction or abscess • Traumatic neuritis • Neurologic, muscular, vascular or bony injury due to incorrect injection site, faulty equipment or technique, • Ineffective vaccine

Immunization error-related reactions can occur as a cluster of events. These events are usually associated with a particular provider, or health facility, or a vial of vaccine that has been inappropriately prepared or contaminated. Immunization error related reactions can also affect many vials. For example, freezing of vaccine vials during transport may lead to an increase in local reactions.

In the past, the most common immunization error was an infection as a result of non-sterile injection. The infection could manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome), or blood-borne virus infection (e.g. HIV, hepatitis B or hepatitis C). However, with the introduction of auto disable (AD) syringes, incidence of infections has reduced significantly. Still, infections can occur during mass vaccinations or disaster situations, particularly if there is a shortage or problem with logistics and supplies or due to unsterile injection practices. This can be avoided by proper planning and monitoring by programme managers.

The symptoms arising from an immunization error may help to identify the likely cause. For example, children immunized with contaminated vaccine (usually bacterium Staphylococcus aureus) become sick within a few hours. Local tenderness and tissue infiltration, vomiting, diarrhoea, cyanosis and a high temperature are the most frequent symptoms. Bacteriological examination of the vial, if still available (maintained in cold chain), can confirm the source of the infection.

Sterile abscesses are rare (~1 per 100 000 doses) local reactions following use of aluminium containing vaccines, especially DTP. Inadequate shaking of the vaccine vial before use, superficial injections and use of frozen vaccines increases the risk of sterile abscesses and of local reactions. Contamination of vaccine or injection equipment can also lead to a bacterial abscess. The vaccines for which open vial policy (refer box below) is applicable, are to be kept as per the defined policy. For BCG vaccine, injection abscesses can arise from improper technique of injection (subcutaneous rather than intradermal injection).

Ignoring contraindications can lead to serious vaccine reactions which may be considered as immunization error. Vaccinators should be clearly aware of absolute and temporary contraindications. Any uncertainty should be referred to a higher-level programme manager or paediatrician or physician. However, it is equally important not to overreact to false concerns of contraindications, which may lead to missed opportunity of vaccination, reduce coverage and, thereby increase the risk of disease in both individuals and the community.

Also, health-care workers need to have a clear understanding of difference between ‘contraindications’ and ‘precautions’. Precautions are not contraindications, but events or conditions to be considered in determining if benefits of the vaccines outweigh the risk associated with its use. This requires an individual, case-based assessment.

Open Vial Policy

Follow Open Vial Policy which is applicable to pentavalent, DPT, Td, Hepatitis B, tetanus toxoid, oral polio vaccine (OPV), Inactivated Polio Vaccine (IPV), pneumococcal conjugate vaccine (PCV) and certain types of rotavirus and JE vaccines. Write date and time of opening of vials. Partially used vials can be used at more than one immunization session up to four weeks of opening the vial provided

- the VVM is in usable stage
- vaccine is not beyond expiry date
- vial has been stored under cold chain during transportation and storage
- the vaccine vial septum has not been submerged in water or contaminated in any way
- aseptic technique has been used to withdraw all doses

To avoid/ minimize immunization errors:

- Vaccines must only be reconstituted with the diluent supplied by the manufacturer.
- In case of reconstituted vaccines, the date and time of reconstitution should be written on the label of the reconstituted vial.
- Reconstituted vaccine should not be used beyond four hours for BCG & measles containing vaccine and two hours for JE vaccine after reconstitution. Any remaining reconstituted vaccines at the end of each immunization session must be discarded.
- In case of vaccines eligible for 'open vial policy', the date and time of opening the vial should be written on the label of the vial
- Other than vaccines, no other drugs or substances should be stored in the refrigerator of the immunization centre.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures for vaccine storage, reconstitution and administration are being followed.
- Adequate attention must be given to possibility of contraindications.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.

Case Studies: Immunization Error Related Reaction	In 2016, in a hospital in country A, three neonates received BCG vaccine from the same vial. All of them collapsed a few minutes following immunization with BCG and expired in a short while. On investigation, muscle relaxant drugs were found in the refrigerator in which vaccines were also kept. It was concluded on case investigation that the probable cause of collapse of these infants was erroneous use of muscle relaxant drug as a diluent for BCG vaccine.

3.3.4 Immunization Triggered Stress Response (earlier immunization Anxiety-Related Reactions)

Individuals and groups can become stressed and react to fear or pain of injection. This reaction is unrelated to the content of the vaccine. Since 2018, a new term "Immunization triggered stress response" has been used to describe immunization anxiety related reactions. This term covers the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety. In this cause specific definition, stress results from the process of immunization. Stress responses are complex, involving a combination of physiological factors within an individual, his or her psychological strengths, vulnerability, knowledge and preparedness and the social context. Such responses may occur more commonly in particular social environments such as peer or occupational groups. Understanding the biological, psychological and social components can help in prevention, diagnosis and management (For details refer to: Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress- related responses following immunization. Geneva: World Health Organization; 2019). For more details, refer to **Annexure 3**. Some manifestations of immunization-triggered stress response are fainting, anxiety, vomiting, abdominal pain, breath-holding, etc.

Fainting is relatively common, particularly in children over five years of age. Fainting is sometimes accompanied by brief clonic seizure activity (i.e., rhythmic jerking of the limbs), but this requires no specific treatment or investigation. It is managed by simply placing the patient in a recumbent position. Recovery of consciousness occurs within a minute or two, but patients may take some more time to recover fully.

Anxiety about immunization can also cause hyperventilation leading to specific symptoms such as light-headedness, dizziness, tingling around the mouth and in the hands. This is especially common in mass vaccination campaigns. During mass campaigns, clusters of mass hysteria is possible, especially if a vaccinee is seen to faint or have some other reaction.

Younger children tend to react differently, with vomiting being a common symptom of anxiety. They may also scream to avoid the injection or run away. Breath-holding may also occur, which can result in a brief period of unconsciousness, following which breathing resumes.

Measures for People at Risk of Vasovagal Reaction

- Immunize in a seated or supine position.
- Use muscle tensing method to prevent vasovagal reaction. Ask the vaccine recipient to clutch a ball in hand of the arm not used for immunization during and after vaccination procedure.
- After immunization, let them remain seated for 15-30 minutes at least.
- A person immunized in a supine position, should adopt an upright position only if they have no vasovagal symptoms.
- Ensure that the session site is arranged in such a manner that chances of injury following fall due to syncope is minimum.

Stress related to immunization can be minimised by giving clear explanation about the immunization. Short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient's line of vision, and privacy during the procedure can reduce anxiety and stress related to vaccination. The following people are at risk of anxiety reactions:

- Young age particularly adolescents.
- Those with a history of anxiety reaction or vasovagal syncope from previous vaccinations/ injections or to the sight of blood or have a phobia of getting injuries.
- Those who have expressed the fear of injections.
- Those who are known to be anxious or with history of acute stress response.
- Those who have received negative information regarding vaccination (from relatives, friends or people they trust, media reports or messages on social media).

Such persons should be identified, reassured and vaccinated in privacy (at least behind a screen). They should be distracted while vaccinating and observed for anxiety reactions (syncopal attacks) soon after vaccination. If necessary, they should be vaccinated in a supine position and should continue to be in the supine position for at least 15 minutes post-vaccination. A trusted familiar person who is himself not anxious or fearful of needle pricks may be present physically with the vaccine beneficiary at the time of vaccination.

It is important to note that fainting attacks (syncope) can be misdiagnosed as anaphylaxis. Health workers should be trained to differentiate between the two conditions. Careful observation and clinical judgment is necessary. Even if a single intramuscular dose of adrenaline is administered to a vaccinee mistaking a syncope as anaphylaxis, the vaccinee is not harmed.

Case Study: Immunization Anxiety-Related Reaction/ ITSR	In 2019, a school-based mass measles-rubella immunization campaign was conducted among 12–19 year old children in country D. On the first day, 44 children were hospitalized with either hyperventilation, vomiting or urticaria. Investigation revealed that two children had generalized urticaria and itching following vaccination. The remaining 42 children had hyperventilation and/or vomiting, suggestive of anxiety reaction. All children were discharged from hospital the same day. While urticaria in the two children was considered to be vaccine product related reaction, clinical features in other children were considered to be immunization triggered stress response.

Prevention and Treatment of Vaccine Reactions

Managing common, minor reactions

Advice on managing the common, minor reactions should be given to parents, in addition to instructions to seek proper medical care if there are more serious symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions. When a vaccine recipient develops a fever, antipyretic drugs, in a recommended dosage and schedule can be given. In case of infants, syrup paracetamol (strength 125 mg/5 ml), in a dose of 10 to 15mg/kg every four to six hours with a maximum of four doses in 24 hours, is recommended for managing pain and reducing fever following vaccinations in the UIP. A febrile child can be cooled with a tepid sponging or bath, and by wearing light clothing. Extra fluids need to be given to children with fever. For a local reaction, cold compresses at the injection site may ease the pain. It is not recommended to give paracetamol prophylactically to prevent expected fever following vaccination. For more details, refer to **Annexure 4**.

Practicing local remedies for any vaccine reaction can risk the health and life of vaccinee and are strongly discouraged. Early medical care by a qualified medical officer will minimize any unwanted outcome and ensure early recovery.

Managing anaphylaxis reactions

A vaccine recipient should be asked to wait for at least 30 minutes following vaccination, so that he can be observed for adverse events such as anaphylaxis or other serious allergic reactions. Anaphylaxis reactions are known to occur rarely in some recipients soon after vaccination. In case of suspected anaphylaxis reactions, a vaccinator should be able to administer one age-appropriate dose of injection adrenaline intramuscularly immediately, followed by transfer of the patient to the nearest AEFI management centre / health facility with a doctor. There should be an anaphylaxis kit with injection adrenaline at all session sites. All vaccinators should be trained to suspect and confidently administer a single dose of adrenaline and transport the patient to the nearest AEFI management centre (**Annexure 5**). It is important to convey to vaccinators that an age-appropriate dose of injection adrenaline administered intramuscularly in suspected cases of anaphylaxis, which eventually turn out not to be anaphylaxis, is safe and does not harm the patient. However, in case of true anaphylaxis, this one dose will be a life-saving intervention. Adrenaline has a short expiry date. Therefore, anaphylaxis kits should be certified once a quarter by the PHC medical officer to ensure availability of injection adrenaline within expiry date. AEFI management centres should have AEFI management kits and the doctor should be trained on managing any adverse event following vaccination using the kit. It is recommended that facilities designated as AEFI management centres should have essential resuscitation equipment such as oxygen cylinders, endotracheal tubes, ambu-bags, etc, to manage emergencies. For more details, please refer to the anaphylaxis guidelines (Operational Guidelines for Initial Management of Anaphylaxis using Injection Adrenaline by ANMs, 2018, MOHFW, GoI).

3.3.5 Coincidental Events

Coincidental events occur after vaccination but are not caused by the vaccine or its administration. Most vaccines are administered during infancy. Underlying congenital illnesses or neurological problems become apparent in infancy and this coincides with vaccinations. Other illnesses and infections are also common during infancy. Many events, including sometimes deaths, occurring during this period may be temporally related to vaccination and be reported as adverse events. These may be falsely attributed to vaccines through chance association. Such events, though temporally associated and manifesting after vaccination, are not caused by either the vaccine or the vaccination. These temporal associations are inevitable given the large number of vaccine doses administered to a large vaccination cohort of millions.

In general, coincidental events are clearly unrelated and but may be blamed on the vaccine by the parents, public or media because of the close temporal association with immunization, especially if the child was previously healthy. Such cases still need to be investigated, to allay public fear and maintain credibility. Responding to public concerns about immunization safety is important for maintaining confidence in the immunization programme. Availability of information on background rates of reported coincidental event may be helpful in the investigation of an AEFI. If the same or similar events also affected other individuals in the same age group and around the same time but they did not receive the suspect vaccine(s), then a coincidental event is more likely. There may also be other evidences showing that the event is not related to immunization.

With increasing awareness of AEFI surveillance, health staff may notify more coincidental events. Also, with introduction of a new vaccine, there is a trend to notify all (any) AEFIs, including coincidental events due to heightened awareness, enthusiasm and training. It is crucial to differentiate these reported coincidental events from potential signals.

Case Studies

1. In response to a severe diphtheria outbreak in country E in 2016, DPT vaccine was provided to children in a mass campaign. During the campaign, a five-year-old girl was reported to have died two days following the receipt of DPT vaccine. The symptoms included convulsions that might have been attributable to a vaccine reaction. Upon investigation, it was found that the girl had a history of convulsions and neurological symptoms unrelated to immunization and the present event was a coincidental event.

2. In 2017, four infants died within 48 hours following administration of pentavalent (DTP-Hep B-Hib) vaccine in country F. Use of vaccine was temporarily suspended. A high-level investigation was carried out, as the deaths had led to public concern, and health staff was reluctant to use the vaccine. Investigation and assessment revealed that out of four cases, three were confirmed as coincidental. One was suffocation and two were due to underlying infections. One was inconclusive.

3. In 2018, the death of a four-month-old infant following DTwP was reported in country G. Within a week, six more cases of severe local reactions were reported with the same batch of DTwP, causing a high public concern and media attention. The implicated vaccine lot was temporarily suspended and replaced with another lot, and a comprehensive investigation was done including toxicity and sterility testing at a national and a WHO-accredited laboratory. Causality assessment confirmed the death as coincidental, but six reported severe local reactions were most likely due to immunization error related reactions.

Deaths Reported Following Vaccination

Table 3.7 below shows a list of countries and the expected number of infant deaths in a day, in a week and in a month as well as the number of DPT/pentavalent vaccinations administered in each country in a day, a week, and a month. Clearly, the number of vaccinations is much more than the number of deaths in a day/week/month. There will be a number of coincidental deaths on the day, week and month after immunization, which is only temporally related to immunization. The actual number of coincidental deaths depends on the population size, infant mortality rate, the number of immunization episodes, and immunization coverage.

When comparing expected versus actual events, it is possible to use statistical analysis to ensure that differences are not simply the result of chance. It is important to also note that the expected number of death calculations presented in the table may be inflated as it is assumed that children who are terminally ill and very ill will still be immunized.

Table 3.7: Estimated Number of Coincidental Infant Deaths - DPT/Pentavalent vaccinations

Country	Infant Mortality rate/1000 live births (IMR)	Number of births per year (N)	Estimated number# of infant death in			Estimated number# of PVV/DTP immunizations* in		
			a month	a week	a day	a month	a week	a day
Bhutan	22	10,000	18	4	1	2200	508	72
Canada	4	3,74,000	125	29	4	83813	19342	2756
China	5	1,08,82,000	4534	1046	149	2436208	562202	80095
India	25	2,31,14,000	48154	11113	1583	5070634	1170146	166706
Indonesia	19	44,96,000	7119	1643	234	992380	229011	32626
Iran	11	12,04,000	1104	255	36	267920	61828	8808
Mexico	11	18,82,000	1725	398	57	418792	96644	13769
Sudan	39	15,34,000	4986	1151	164	331689	76544	10905
United Kingdom	4	6,77,000	226	52	7	151716	35011	4988

#Coincidental Infant Deaths that could be temporally linked

Note: All data are estimates as in 2021. Assumes uniform distribution of deaths and immunization over the time period.

*The assumption here is a three-dose schedule for either DTP or pentavalent vaccine with 90% coverage for each dose.

Source: Annual number of births (Table 1. Demographics), infant mortality rates (Table 2. Child mortality) and % DPT-3 coverage (Table 4. Child health) in 2021 from The State of the World's Children 2023: For every child, vaccination, UNICEF Innocenti – Global Office of Research and Foresight, Florence, April 2023. (https://data.unicef.org/resources/sowc-2023/)

3.4 AEFIs Following COVID-19 Vaccines

COVID-19 vaccines were developed and deployed rapidly within months to protect at-risk priority populations in order to reduce mortality and morbidity due to COVID-19. Drug

regulators were empowered to grant Emergency Use Authorizations to enable expedited availability of COVID-19 vaccines to people affected by a public health emergency. Under this, some phases of clinical trials for COVID-19 vaccines were conducted simultaneously. Many of the COVID-19 vaccines were developed using new or rarely used vaccine technology / platforms. Due to these reasons, limited information was initially available on the adverse events of these vaccines in the initial stages of mass vaccination. Vaccine safety reviews and benefit-risk analysis need to be frequently conducted to elicit issues requiring action.

Common minor adverse events reported following COVID-19 vaccines used in the country are pyrexia, injection site pain, swelling and redness, headache, dizziness, vomiting, fatigue, hypersensitivity etc. Serious adverse events such as Thrombosis with Thrombocytopenia Syndrome (TTS) (formation of large blood clots in combination with low platelet counts) have been observed at a frequency of less than 1 in 100,000 vaccinated individuals following adenovector – based COVID-19 vaccines in India. Based on the adverse events reported during clinical trials and following previous use of same vaccine platform for other vaccines, certain adverse events are identified for monitoring during the roll out of the new vaccine. These events are called Adverse Events of Special Interest (AESI). For COVID-19 vaccines in India, studies are underway to monitor the risk of specific events identified for their potential association with use of COVID-19 vaccines. Some of the identified events are myocarditis, pericarditis, encephalitis, myelitis, seizures, idiopathic thrombocytopenia, Guillain-Barré Syndrome, thrombosis with thrombocytopenia syndrome and thrombosis. Based on the evidence available on the safety and efficacy of the COVID-19 vaccines, these vaccines have been found to have a favorable benefit to risk ratio.

Summary

- Adverse events may occur due to some inherent properties of the vaccine (vaccine product-related reaction), due to a defect in manufacturing (vaccine quality defect-related reaction) or due to immunization error related reactions.
- Immunization triggered stress responses (earlier referred to as Immunization anxiety-related reaction) are common, and are due to fear or pain of injection rather than the vaccine itself.
- Immunization error-related reactions (previously classified as “programme errors”) are avoidable.
- At times, the event may be unrelated to immunization, but may have a temporal association (coincidental event).
- Antigen/vaccine-specific background rates of vaccine reaction are useful to guide decision-making on classification of vaccine related reactions.
- Minor vaccine reactions are common and do not require special treatment. Rare, serious vaccine reactions need a timely treatment by qualified medical personnel.
- With novel vaccines it is important to monitor adverse events of special interest for their potential association with vaccines.

4 Recording and Reporting AEFIs

4.1 Who can Inform about an AEFI Case

The government's Universal Immunization Programme (UIP) is the main service provider for childhood immunization in India. Immunization sessions are conducted in government-managed centres in primary, secondary and tertiary care institutions on fixed days (which vary in individual states) at least once a week. In India, most of the routine immunization services are provided through outreach sessions within the public health sector. The private sector also contributes to routine childhood immunization and offers non-UIP vaccines in addition to routine immunization services.

In most of the cases, patients themselves, or family members, maybe the first to suspect an adverse event. On suspecting an AEFI, they may inform the vaccination service provider or a health care service provider. If there has been a death, hospitalization, events occurring in clusters, or there is a lack of action by the service providers, the patient or his family member may inform the local people's representatives or even the local media.

Any healthcare provider (public or private) who comes across any adverse event following immunization has the responsibility of informing the district health authorities (District Immunization/RCH Officer) either directly or through a government medical officer.

In Rural Areas

The following healthcare providers may be the first ones to be informed of an adverse event following immunization (AEFI) or who may suspect/identify an AEFI:

1. Frontline workers such as Accredited Social Health Activists (ASHA) and anganwadi workers (AWW)
2. Vaccinators such as Auxiliary Nurse Midwife (ANM), male multipurpose health workers and their supervisory staff (Lady Health Visitor (LHV), Health Supervisors), etc.
3. Medical Officers (MOs) and other paramedical staff of Health and Wellness Centres (HWCs), Primary Health Centres (PHCs) and Community Health Centres (CHCs).
4. Doctors and staff nurses working in private clinics, dispensaries, nursing homes and hospitals.
5. Media, lay public and community mobilizers can also report AEFIs.

In Urban Areas

Medical officers, staff nurses and other paramedical staff in a wide range of healthcare institutions may be the first to suspect/identify or be informed of an AEFI. These personnel may be working in:

1. Dispensaries, urban health centres and maternal and child health centres under urban local bodies (municipalities and corporations).
2. Government sub-divisional, divisional and district hospitals.
3. Government and private medical colleges (including staff of the Adverse Drug Reaction Monitoring Centres under the Pharmacovigilance Programme of India).
4. Health care facilities run by the central government or public sector organizations such as the CGHS, Railways, Defence, Employees' State Insurance (ESI) Corporation, airport authorities (vaccination for international travel), other industry and autonomous bodies.
5. Private healthcare providers – practitioners, paediatricians, obstetricians-gynaecologists, physicians, neonatologists, and other clinicians/specialists in secondary and tertiary care hospitals.

It is the responsibility of the District Immunization Officer to ensure that the above listed health cadres in the public and private health sector are sensitized to suspect, identify, notify and report AEFIs to the DIO. Special focus is required to orient doctors and staff in secondary and tertiary care hospitals in government and private sector especially in medical colleges and large speciality/super-speciality hospitals.

The DIO should ensure that all AEFIs following any licensed vaccine, whether administered in the UIP programme or outside of it (tetanus toxoid, rabies, yellow fever, etc.) or in private sector (influenza, chicken pox, mumps, etc.) in India should be reported.

4.1.1 Who should be Informed/Notified about an AEFI case?

An AEFI can be minor or it can be serious (death, hospitalization, events in clusters, etc.) or severe in nature. The action to be taken by the first person who is informed of an AEFI depends on whether it is minor or severe/serious. Serious/severe AEFIs are immediately notified to the Medical Officer of nearest government PHC, CHC and/or the District Immunization Officer (DIO) by quickest means of communication e.g., telephone, SMS, WhatsApp, email, messenger, etc. The most important reason for immediately notifying a serious/severe AEFI to the medical officer or the DIO is to ensure treatment is provided to the AEFI case on priority. Once treatment has been initiated, the process of reporting and investigations can begin. Minor events are recorded in AEFI registers. Channels of reporting have been discussed further in this chapter.

It is of paramount importance that an AEFI case be provided with appropriate medical management without delay

4.2 Reporting of AEFIs

There are two channels of reporting AEFIs in the government system

1. Immediate reporting of serious and severe AEFIs
2. Routine reporting of all types of AEFIs – minor, severe and serious

4.2.1 Immediate Reporting of Serious and Severe AEFIs

A serious or severe AEFI case needs to be reported immediately to the concerned Medical Officer or the DIO due to clinical severity and potential threat to public confidence in the immunization programme. Immediately after the identification/notification of a serious and severe AEFI, a two-step process has to be initiated.

Step 1: Reporting serious and severe AEFIs to the appropriate authority (DIO or MO in charge of an urban area & DIO or MO I/C of the health centre in rural area)
Step 2: District-level investigation of reported serious and severe AEFI

All notified serious/severe AEFI should be documented on a CASE REPORTING FORM (CRF) (**Annexure 6**) and submitted to SAFE-VAC as soon as possible. SAFE-VAC is a web-based application for recording and reporting of serious / severe AEFI cases. The cases will be entered by the DIO in SAFE-VAC (Co-WIN SAFE-VAC for AEFIs following COVID-19 vaccination) and can be accessed and monitored at the state and national levels.

Surveillance and Action for Events Following Vaccination (SAFE-VAC)

In a move to digitize the AEFI surveillance processes, MoHFW conceptualized the development of a web-based application named Surveillance and Action for Events Following Vaccination (SAFE-VAC). This can be accessed at https://safevac.mohfw.gov.in Currently data regarding AEFIs can be entered into SAFE-VAC by the DIOs, SEPIOs and national level. They can monitor the progress by analyzing the data and take appropriate corrective measures.

Objectives of SAFE-VAC

- To speed-up the processes of recording/ reporting which will shorten the response time following AEFI
- To reduce data loss and time taken while transmitting the AEFI data
- To support timely investigation and causality assessment process for the reported AEFI cases
- Improve timely feedback and action based on evidence generated from data.

Benefits of SAFE-VAC

- Improves timeliness and completeness of AEFI reporting
- Reduces loss of information during transmission to higher level
- Allows cross-notification of cases from district to district
- Reduces loss of data due to change of DIO / data handler
- Empowers district and state authorities to monitor and track the progress
- Provides easy and secure access to information to programme managers
- Facilitates early causality assessment
- Promotes evidence-based action for better vaccine acceptance.

For COVID-19 vaccination, another version of SAFE-VAC was developed and integrated to Co-WIN application. The information submitted in SAFE-VAC is collated and can be accessed at state and national level. It will help state and country offices to monitor reporting, status of document completion and causality assessment of cases. Additionally, inbuilt analysis can be used by the state and national level AEFI committees and programme managers for useful insight and decision making.

All serious and severe AEFIs should be treated as a medical emergency and priority should be given to its management followed by reporting and investigation in the standardized AEFI formats. A list of reportable AEFIs that may occur after vaccination is available in Table 4.1. The list is only indicative and not exhaustive.

Table 4.1: List of Adverse Events Known to be Associated with Vaccines

Vaccines	Reaction
BCG	**Local:** Local abscess, Keloid, Cutaneous skin lesions, Lymphadenitis, Suppuration **Systemic:** Osteitis, Osteomyelitis, Disseminated BCG disease, Immune Reconstitution Syndrome (HIV patients)
OPV	Vaccine Associated Paralytic Poliomyelitis (VAPP)
DTwP/ Pentavalent (DTwP+HiB+HBV	Fever >38°C, Irritability, Drowsiness
	Prolonged inconsolable Crying (>1 hr) High Fever >40.5°C Acute Encephalopathy/Encephalitis, HHE, Seizure, Anaphylaxis/Shock
DTaP/ DTaP+Hib+HBV	Fever >38°C and Irritability, Drowsiness
	Prolonged Inconsolable Crying (>1 hr) High Fever >40.5°C
	Hypotonic hyporesponsive episodes, Seizures, Anaphylaxis
Hepatitis B	Anaphylaxis
Measles/MR	Fever >39.4°C, Rash, Febrile Seizure
	Thrombocytopenia, Anaphylaxis, Encephalopathy/Encephalitis/ Encephalomyelitis
Rubella	Arthralgia/Arthritis/Arthropathy
Mumps	Aseptic Meningitis
MMR vaccine	Febrile seizure
Tetanus/ Td	Brachial Neuritis, Anaphylaxis
Rotavirus	Intussusception
Japanese Encephalitis	Serious allergic reactions, Seizures, Encephalopathy, Neuropathy, Myelitis, Aseptic meningitis
Influenza (Inactivated)	Anaphylaxis, Guillain-Barré Syndrome, Oculo-Respiratory Syndrome
Influenza (Live attenuated)	Seizures, Anaphylaxis, Wheeze, Guillain-Barré Syndrome
Varicella zoster	Febrile seizures

HPV	Myalgia, Arthralgia, Anaphylaxis
Rabies	**Local reactions:** Pain, Redness, Swelling induration **Systemic reactions:** Fever, Headache, Dizziness, Gastrointestinal symptoms **Hypersensitivity reactions** (Arthralgia, Angioedema): Anaphylaxis, Guillain-Barré Syndrome
Yellow Fever	Headache, myalgia, Malaise, Fever, Injection site pain, Swelling
	Viscerotropic disease, Neurotropic diseases (Encephalitis, Meningitis, Guillain-Barré Syndrome)
Typhoid	**Oral**: Gastrointestinal, Fever **Injectable**: Injection site pain, Erythema, Induration, Headache
COVID-19 vaccines	Anaphylaxis
COVISHIELD	Thrombotic Thrombocytopenia Syndrome (TTS)
	Thrombocytopenia

4.2.2 Routine Reporting

This includes reporting of all AEFIs from the point of occurrence of the AEFI (health staff at the periphery) up to the national level through various methods:

1. **AEFI registers at healthcare facility / block / planning unit level:** All ANMs of a block or planning unit should record all AEFIs (serious, severe and minor) informed to them from their respective areas on weekly basis and document them in an AEFI register (**Annexure 7**) maintained at the centre. AEFI registers should also be maintained at all private and public healthcare facilities such as nursing homes, district hospitals and medical colleges under the supervision of a nodal medical officer. Healthcare staff of the facility including vaccinators, nursing, para-medicals and doctors can enter AEFIs in this register.

   The AEFI register notifies basic information of all AEFIs in a simple format and this needs to be verified by the Medical Officer In-charge (MO I/C) every week. The MO I/C of the block or planning unit (PHCs, CHCs etc.) should analyse the information regularly to look for any pattern or preventable programme errors using an assessment format (part of **Annexure 7**) and will submit the same to DIO of the district every month. In the assessment format, the data related to minor and serious/severe AEFIs under each sub-centre area will be analysed for patterns leading to further investigations or actions such as more frequent monitoring of cold chain, vaccination sessions, trainings, etc. depending on the types of AEFIs reported and/or presence of clustering.

2. **Monthly Progress Reports (MPR):** It is a monthly reporting system using existing immunization monthly reporting formats that may vary from state to state (such as NRHM, HMIS, etc). In the current HMIS system, there are formats for reporting of various data

primarily related to RCH from facilities specifically sub-centers, PHCs/wellness centres, CHCs, sub-divisional hospitals, district hospitals and medical colleges. Sub-centre-wise data is entered at the PHC level. Data from all PHCs, CHCs, SDHs, DHs and medical colleges are visible at the district level and then at the state level, see Figure 4.1.

In case of sub-centres (HWC-Sub-centre), the number of AEFI cases reported during the month is recorded under section 8.6 Adverse Event Following Immunization (AEFI). There are four rows under this section as follows:

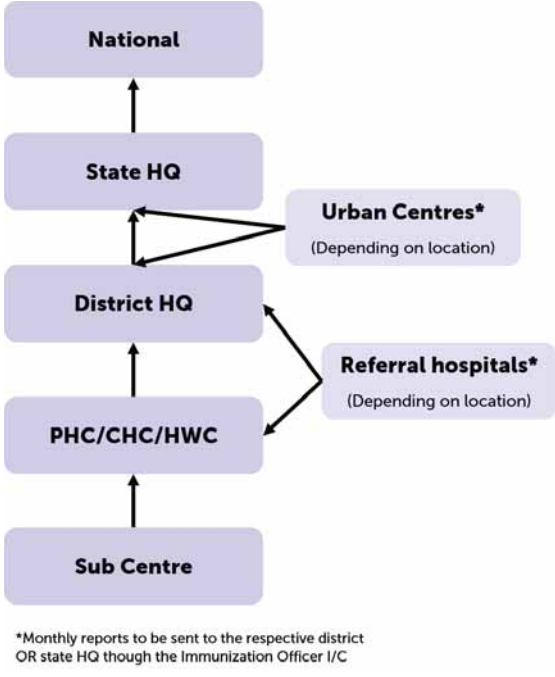
8.6.1. Number of cases of AEFI -Minor (e.g. fever, rash, pain, etc)

8.6.2. Number of cases of AEFI - Severe (e.g. anaphylaxis, fever>39°C, not requiring hospitalization, etc.)

8.6.3. Number of cases of AEFI - Serious (e.g. hospitalization, death, disability, cluster, etc.)

8.6.3.a. Out of Number of cases of AEFI - Serious, total number of AEFI deaths

Figure 4.1: AEFI Monthly Reporting - Data Flow



Please note that deaths (reported under 8.6.3a) will also be reported under 8.6.3. ANMs should enter 0 in the relevant row in the formats, if no AEFI has been reported. The numbers need to be entered separately for "In facility" and "Outreach", as may be the case. The same section and rows are numbered 9.6 (9.6.1, 9.6.2, 9.6.3, and 9.6.3a) in the formats for PHC, CHC, SDH, DH and medical colleges. AEFI registers should be analysed to ensure that the correct number of AEFIs are reported in HMIS for PHCs, CHCs, SDHs, DHs and MCs. Medical colleges may need initial handholding/guidance for reporting AEFIs in HMIS. Relevant sections for reporting of AEFIs is HMIS formats is displayed in Figure 4.2.

Figure 4.2: Reporting of AEFIs in HMIS Monthly Service Delivery Formats

Monthly Service Delivery Reporting format

HWC-Sub Centre (HWC-SC) FORMAT

Facility Code	Data Item	Numbers reported during the month (In-facility)	Numbers reported during the month (Outreach)
8.6	**Adverse Event Following Immunisation (AEFI)**		
8.6.1.	Number of cases of AEFI -Minor (eg.- fever, rash, pain etc)		
8.6.2.	Number of cases of AEFI - Severe (eg.- anaphylaxis, fever>102 degrees, not requiring hospitalization etc.)		
8.6.3.	Number of cases of AEFI - Serious (eg.- hospitalization, death, disability , cluster etc.)		
8.6.3.a	Out of Number of cases of AEFI - Serious , total number of AEFI deaths		

Monthly Service Delivery Reporting format

HWC-Primary Health Centre (HWC-PHC) FORMAT

Facility Code	Data Item	Numbers reported during the month (In-facility)	Numbers reported during the month (Outreach)
9.6	**Adverse Event Following Immunisation (AEFI)**		
9.6.1.	Number of cases of AEFI -Minor (eg.- fever, rash, pain etc)		
9.6.2.	Number of cases of AEFI - Severe (eg.- anaphylaxis, fever>102 degrees, not requiring hospitalization etc.)		
9.6.3.	Number of cases of AEFI - Serious (eg.- hospitalization, death, disability , cluster etc.)		
9.6.3.a	Out of Number of cases of AEFI - Serious , total number of AEFI deaths		

4.3 Reporting and Investigating Serious AEFIs - Process, Forms & Timelines

Before the procedure of reporting & investigating serious and severe AEFIs is defined, it is important to mention a few important definitions:

Notification: When a health care service provider is informed by a vaccine beneficiary or his caregiver of an AEFI, the health worker or frontline worker or private practitioner, or a doctor in a health institution such as a hospital or medical college should notify the case to the Medical Officer of the PHC (in case of the health worker or frontline worker) or the DIO (in case of a private practitioner or a doctor in a health institution such as a hospital or medical college). Notification can be done by any means like a phone call, SMS, WhatsApp, Email, etc.

Reporting: It is the process of sending information about an AEFI to the district and documentation of the same in the Case Reporting Form (CRF). A hard copy of CRF is filled by

the Medical Officer (MO) and sent to the District Immunization Officer. In the case of large hospitals and medical colleges, the CRF should be filled with as many details available and shared with the DIO through the AEFI Nodal Officer of the hospital or medical college.

The following forms are used for reporting and investigation of any notified serious or severe AEFI:

1. Case Reporting Form (CRF)
2. Case Investigation Form (CIF)

A. DISTRICT LEVEL

AEFI CASE REPORTING FORM (CRF) (only for serious/severe AEFIs)

The CRF captures basic minimal information pertaining to the following:

1. Reporter (Section A)
2. Patient (Section B)
3. Vaccine (and diluent) (Section C)
4. Event (Section D)
5. Decision making (Section E)

Purpose:

- It provides basic information of the event for decision making at all levels and is therefore urgent.
- It should be carefully completed with as many details as possible, because investigation of the case is planned based on the information in the CRF.
- A properly filled CRF helps identify potential vaccine safety signals early without waiting for completion of investigations and causality assessments.
- CRF is the first reference point for quality assurance and performance of the immunization programme and therefore can provide information on the overall quality of the health system.

Process and Timeline for Reporting Serious/ Severe AEFIs

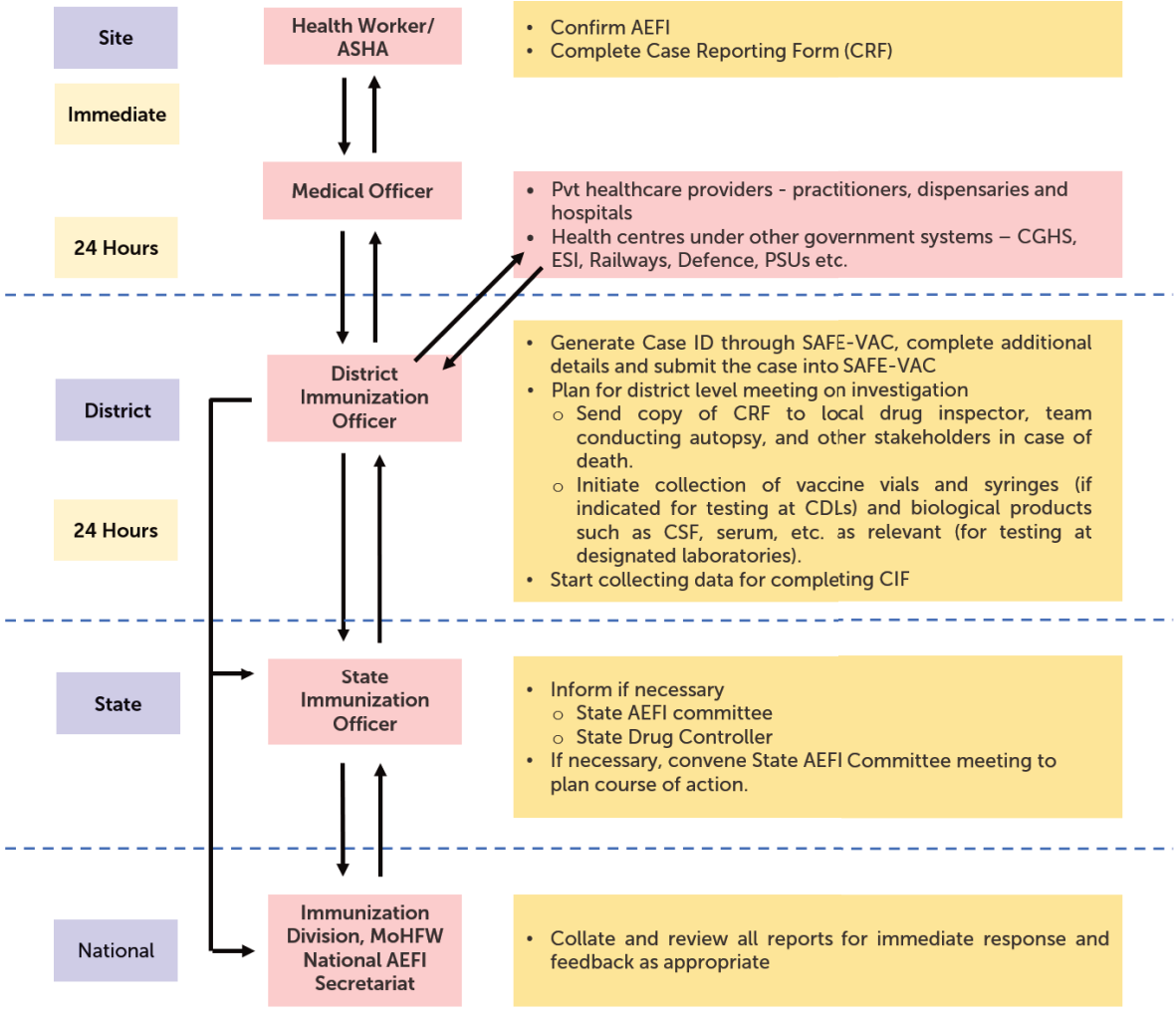
Steps in completing Case Reporting Form (CRF), see Figure 4.3

Preliminary steps and decision making:

1. A serious or severe AEFI cases can be reported using the CRF (in hard copy) from any level in the government or private sector. The reporting doctor / medical officer will enter information in "Section A", after receipt of information from any source including ANM, AWW, ASHA, ICDS, Health Supervisor, community mobiliser, private practitioners, clinicians in tertiary and secondary care hospitals and clinics, lay public, informal health practitioners such as RMPs, ADR Monitoring centres, media reports, etc. The MO should visit the AEFI case for examination and to ensure treatment of the case.
2. The medical officer should examine the patient and complete sections B, C and D of the CRF and submit the CRF to the DIO within 24 hours of notification. In case of a reported unexplained death, the medical officer should make all efforts to ensure a post-mortem is conducted at the earliest.

3. Within 24 hours of receipt of CRF, the DIO should review the CRF sent by the MO and:
   (a) complete the details in "section E" by providing district specific information (contact details).
   (b) generate Case ID from SAFE-VAC and write it manually on hard copy of CRF.
   (c) enter the case details in the SAFE-VAC portal and upload the scanned copy of CRF and other available documents. If difficulty is faced during data entry in SAFE-VAC, email request may be sent to aefiindia@gmail.com.
   (d) plan immediate investigation of the AEFI case with the help of members of District AEFI Committee.
   (e) plan conduct of verbal autopsy as per the guidelines in case of death, as soon as possible.

Figure 4.3: Case Reporting Form - Process, Timelines and Actions



4.3.1 Planning for Investigations

1. DIO should convene a meeting of the District AEFI committee and determine the need for conducting a time bound investigation and decide the further course of action.
2. The MO in consultation with the DIO should prepare a list of items relevant to that particular event that would assist the investigation team such as the relevant registers, ANM diaries,

session tally sheets, indent records, used and unused vials, diluents and syringes.

3. The MO and DIO should ensure that such articles and items are preserved and are available at the time of filling up the case investigation form by the members of the investigation team from district level.
4. Copies of the completed CRF should be shared with:
   - District AEFI committee
   - Drug Inspector (who is also a part of the AEFI committee)
   - In case of death, a copy of the CRF should be provided to the panel conducting the post-mortem and the verbal autopsy.
   - Conducting a verbal autopsy in all death cases is mandatory. This is to be done even if a post-mortem has been conducted.
   - The testing laboratory along with Laboratory Request Form (LRF) and other documents (as outlined in chapter "Laboratory aspects of AEFI"), in case the District AEFI committee decides to send the samples of implicated vaccine/ diluents/ logistics or biological products for testing.

Specimens for testing must be collected as soon as possible as outlined in the chapter on Specimen Collection and Handling for AEFIs. The collected samples may be sent only if recommended by the district AEFI committee.

B. Role of State Immunization Officer

On receipt of completed CRF through SAFE-VAC at state level, the state immunization officer should decide on the gravity of the AEFI case(s) and accordingly take a decision either to provide immediate support to the district through the State / regional AEFI committee (including state drug controller) at this stage or wait for the report of the investigation carried out by the district and submitted in the CIF.

C. Role of Immunization Division, MoHFW, Government of India

At the national level, the National AEFI Secretariat at MoHFW will review, collate and provide technical feedback to Immunization Division, MoHFW, Government of India who may recommend further action based on the gravity of the AEFI case (s). This action may include involvement of the DCG(I)/CDSCO and National AEFI Committee at this stage or wait for additional information before charting out a course of action.

CASE INVESTIGATION FORM (CIF) (Annexure 8)

Content of the CIF: The Case Investigation Form (CIF) captures in-depth information about the reported AEFI case as well as the circumstances of its occurrence. Additional information that can be obtained during investigation can be included as addendum if the investigators feel that this information will support evidence of causality.

(a) Basic details
(b) Relevant patient information (health and socio-demographic) prior to immunization
(c) Details of first examination of severe and serious AEFI case
(d) Details of medical care sought and treatment provided
(e) Details of vaccines provided at the vaccination site

(f) Immunization practices at the places where concerned vaccine was used
(g) Cold chain and transport facilities
(h) Community Investigation
(i) Other key findings
(j) District AEFI Committee Review and Investigation Report
(k) Any other information, that may support the evidence of causality

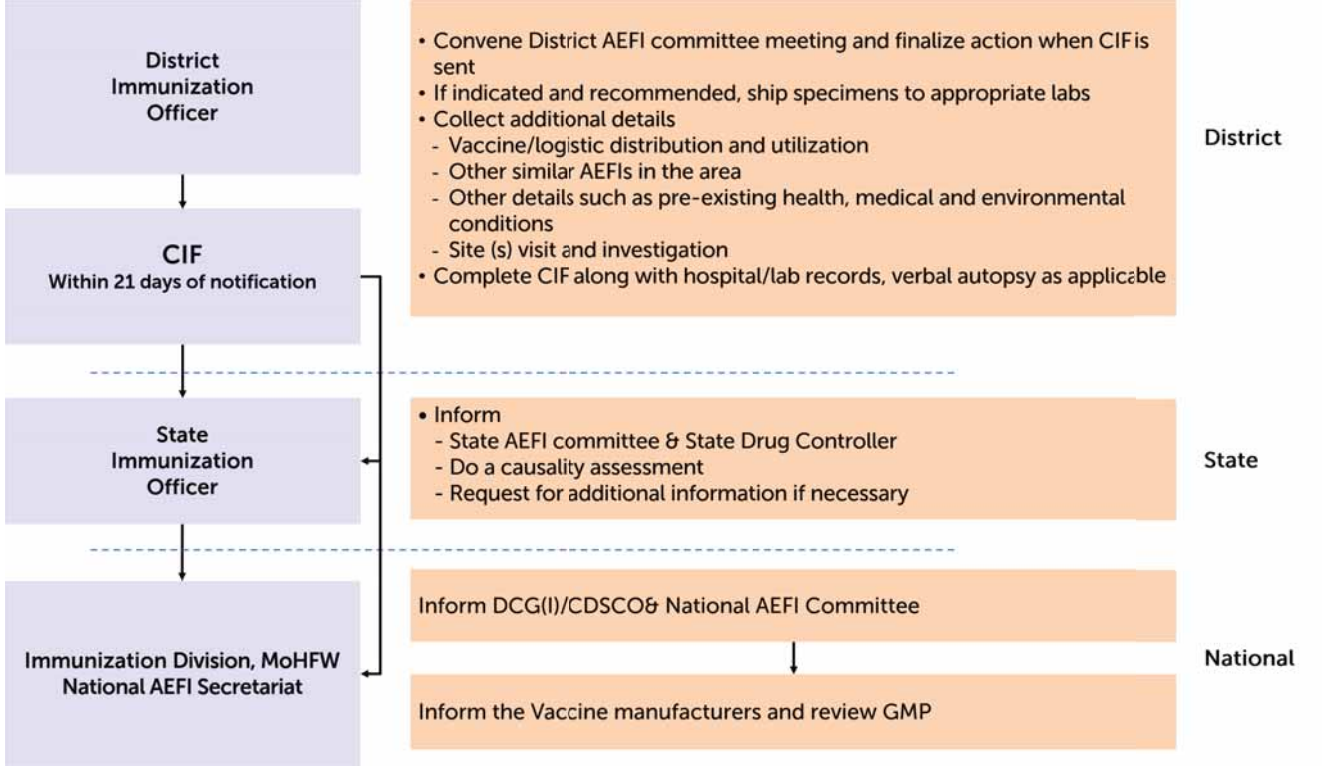
Purpose: The CIF will guide the investigating team to collect important information required for causality assessment of the AEFI and should be as detailed as possible.

Note: It is important to remember that the CIF is not a "set in stone" document. Information beyond what is listed in the CIF or which has been received using non-conventional methods can be included in the CIF. An example is suspicion of suicide or homicide based on information provided by neighbours/relatives; use of drugs, alcoholism, etc.

Process and reporting timelines of investigations

Case Investigation Form (CIF): The CIF form is to be used for providing a structured report of the AEFI investigation carried out by the District AEFI Committee (see chapters 5 and 6 for AEFI investigation). The DIO will submit the completed CIF along with other supporting documents including a verbal autopsy in case of AEFI deaths into SAFE-VAC for simultaneous transmission to state and national level as early as possible or within 21 days of case notification (see Figure 4.4)

Figure 4.4: Case Investigation Form (CIF) - Process, Timeline and Actions



Steps for completing Case Investigation Form (CIF)

A. DISTRICT LEVEL

Role of the DIO

1. DIO should discuss and coordinate with the District AEFI committee to plan the investigation and complete all details mentioned in the CIF including:
   (a) Vaccine cold chain, logistics, distribution and utilization (including batch number, lot number, details related to vials used as per open vial policy, etc.)
   (b) Other AEFI in the area, clustering if any
   (c) Other details such as pre-existing health, medical and environmental conditions both in the case(s) as well as the area
   (d) Verbal Autopsy to reveal the underlying socio-demographic factors, in all death cases

2. While completing the CIF, the DIO should ensure that the relevant samples have been sent, if required, as part of the investigation including vaccine samples, syringes and injections. In addition, reports of appropriate samples (if sent) should also be shared for establishing a clinical diagnosis.
3. The DIO should organize the field investigation of the AEFI with assistance of the District AEFI Committee as outlined in the chapter on AEFI investigation. DIO should ensure compilation of all relevant documents including clinical records, hospital records, lab results of urine/blood/CSF etc, post-mortem and verbal autopsy report, reports of vaccine and syringe sample tests (if sent) from the certified laboratories. A revisit to the case may be planned if warranted.
4. The District AEFI Committee should then summarize the AEFI report in the context of the findings of these tests and frame a provisional diagnosis of the AEFI case. The DIO should then complete the Case Investigation Form (CIF) with assistance of the District AEFI committee, should obtain the committee's endorsement and submit the same in SAFE-VAC within 21 days of the notification of event. It is quite possible that few important documents of the case, for example, complete post-mortem report or laboratory reports of vaccine samples etc are not available within stipulated period of 21 days. Therefore, a period of 45 days after notification has been provided to the district for submission of pending reports, if any; even though CIF has been submitted by the district within 21 days.

In Urban areas, the DIO's counterpart would be the Medical Officer Health in charge of Immunization such as the Corporation Immunization Officer, Municipal Health Officer, etc. The roles and responsibilities of the urban counterparts will be the same as the DIO for detection and responding to AEFIs.

Please note: It is never appropriate to discontinue immunization while awaiting the completion of the AEFI investigation.

B. STATE LEVEL

Role of State Immunization Officer

The state immunization officer will coordinate with the state AEFI committee which includes the State Drug Controller, for review of the CIF and the supporting documents and will decide further course of action. Deaths and clusters should be taken up as a priority for review. The state AEFI committee should undertake a causality assessment of the event, taking into consideration the state experience with the vaccine(s). If necessary, state may request for additional information such as laboratory tests, field visit information, etc. It is expected that the causality assessment of a serious case will be conducted by the state AEFI Committee within 100 days of case notification.

C. National Level

Role of Programme Manager at the Immunization Division, MoHFW, Government of India and National AEFI Secretariat

At the national level the AEFI Secretariat will be responsible for compiling, collating and reviewing all reports of AEFIs from the districts. The Secretariat will summarize and update the information and share weekly updates with other vaccine pharmacovigilance stakeholders including DCG(I) and PvPI-IPC. The Additional Commissioner, Immunization Division, MoHFW, Government of India will share the available information of serious and severe AEFIs with other senior officers in the Ministry of Health and Family Welfare. The DCG(I) may inform the drug manufacturers and review Good Manufacturing Practices if required.

4.4 AEFI Records and Databases

District and State level: The DIO and State Immunization officer should review the database of all reported AEFIs and line list in SAFE-VAC. A quarterly review of data of all serious / severe AEFI should be done by the district and state AEFI committee. This will help the district and state to take appropriate action and improve AEFI surveillance. Feedback should be provided to all stakeholders.

National level: The National AEFI Secretariat maintains the national level AEFI database, both manually and digitally (SAFE-VAC), at the MoHFW. It is regularly updated following receipt of reporting formats.

Periodic routine data analysis should be carried out at the district, state, and the national level. The monitoring of reported data includes the following information:

- Number of AEFIs reported
- Geographic and temporal distribution of AEFIs reported (look for clustering) and epidemiological analysis of the same
- Number and type of adverse events reported by antigen (e.g. Injection site abscess, seizures, HHE, etc.).
- Geographic distribution of possible programme related adverse events like abscess
- Clustering of adverse events according to vaccine, batch, etc.

- Timeliness and completeness of reporting
- Silent blocks/corporation/districts/states not reporting AEFI data.

Appropriate corrective actions must be planned at all levels, periodically; on the basis of review of monitoring data. Please refer to the chapter 9 on AEFI Committees for further details on indicators and analysis for AEFI Surveillance.

4.5 Reporting of Cluster AEFI Cases

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place, vaccinator or vaccine administered. A cluster of AEFI cases is a specific condition which warrants immediate investigation because of its nature and seriousness. An AEFI cluster can happen after a routine immunization session or a campaign session.

Though an AEFI cluster is investigated as a special entity, the guidelines and procedure for reporting and recording of cases of an AEFI cluster will remain the same with some modifications. Each case belonging to a cluster will be reported and investigated using separate CRFs and CIFs and submitted to SAFE-VAC. A summary of the investigations conducted should be prepared describing the sequence of events, common factors, etc., leading to an understanding of cause of the events in the cluster. Details of deaths reported as part of the cluster should be well described. A linelist with details of all cases of the cluster should mandatorily be a part of the summary. The linelist should have age, gender, vaccines received, sequence of vaccination (if known), onset of symptoms, date and time of hospitalization and death, signs and symptoms, etc. During mass campaigns, special directions will be shared by MOHFW for a revised protocol to report and record findings of investigations of cluster cases related to anxiety. These will be valid only for the duration of the campaign.

4.6 Reporting of Cross-Notified AEFI Cases

It is important to note that an AEFI case belongs to the area (village / urban area / district / state) where the concerned case was immunized. It is the place of vaccination which decides the district an AEFI case belongs to and not the residence of the case or place of treatment or place of reporting.

If a district is informed about a case which belongs to another district, the case needs to be cross-notified to the parent district. In such case, the reporting district will cross-notify the case to parent district through SAFE-VAC. The reporting district will fill the CRF with the available information, will generate Case ID using "cross-notification" functionality of SAFE-VAC, will fill the information under its Case ID in SAFE-VAC and upload the scanned copy of filled CRF. Then, the parent district will complete the information gap in this CRF (example: information about vaccines administered, exact address of the vaccination site, any more similar cases, etc.) and will submit the case in SAFE-VAC. In SAFE-VAC, reporting district can generate Case ID for a cross-notified case, fill the information and upload the documents, but final submission can only be done by parent district. Please refer to SOPs of SAFE-VAC for details on cross-notification of cases.

It is the responsibility of the reporting district to support parent district by providing available information of the case like medical records, post-mortem report etc. It is the parent district which will conduct investigation of the case and will collect the information related to vaccines and their batches used for vaccination of concerned case, concerned immunization session and techniques, cold chain points etc.

4.7 AEFI Notification by a Private Health Facility/ Practitioner

The State and District authorities (DIO/ CMO or the Block MO) should ensure that the key nodal persons are identified from all private health facilities and sensitized about the AEFI reporting and surveillance system and are encouraged to notify AEFI timely. AEFI reporting is to be encouraged for not only the vaccines supplied by the Government of India but for all vaccines being used in the private sector, including the new vaccines. The reporting formats and channels, processes of investigations, assessments and timelines for adverse events following use of vaccines in the private sector remain the same. Therefore, a private practitioner or health care facility can inform/notify an AEFI case to concerned government MO/DIO through available reporting channels. Thereafter, the case should be investigated by the district health authorities. To encourage further reporting, appreciation for reporting cases as well as feedback of AEFI investigation and causality assessment should be provided to the reporting facility. Professional bodies like IAP, IMA, IPHA, partner agencies like WHO-NPSN, UNICEF, UNDP, USAID, PATH and others should also be encouraged to support AEFI surveillance.

For ease of notification of AEFIs by private practitioners, National AEFI Committee will explore additional possibilities to improve reporting. MoHFW will provide a feasible, easy and secure channel for reporting AEFIs by private practitioners and will notify the same. MoHFW will also coordinate with national offices of professional bodies (IAP, API, IMA etc.) and all relevant stakeholders to sensitize private practitioners and improve reporting.

4.8 AEFI Notification by Health Systems

Vaccinations are conducted in health centres or vaccination centres under other government ministries, departments and autonomous bodies – Central Government Health Services (CGHS), Employees' State Insurance (ESI) Corporation, Railways, Defence, Airport Authority, PSUs etc.

The AEFI reporting from these bodies is integrated into and is part of AEFI surveillance system of the country. The DIOs will identify such health institutions and centres in their respective areas and will liaison with them. A nodal person for AEFI surveillance will be identified in each health centre/facility, who will report AEFI cases to concerned DIO or MO I/C. The reporting forms and channels will remain the same.

All such health institutions and centres will also maintain AEFI registers under the supervision of nodal person and the guidance of DIO / MO in-charge. The DIO will organize refresher/sensitization meetings for health workers and medical officers of these centres from time to time.

4.9 AEFI Reporting by ADR Monitoring Centres

Adverse Drug Reaction (ADR) Monitoring Centres in the network of the Pharmacovigilance Program of India (PvPI)

The State and District authorities (DIO/CMO or the Block MO) should ensure that designated ADR monitoring centres (AMC) of the PvPI and their respective coordinators are aware of the contact details of MO/DIO for reporting an AEFI. These centres must be encouraged to assist the AEFI surveillance system in reporting and investigation of AEFIs. The case notification form (CNF) used by AMCs to report serious AEFI cases is in **Annexure 9**. As the information of an AEFI case is received by DIO through CNF, the DIO should immediately initiate reporting and investigation of case as per defined process. Appreciation for reporting AEFI cases as well as coordination for AEFI investigation and causality assessment should be undertaken by the state and district authorities.

4.10 Reporting of Minor AEFIs

Currently, name-based reporting of minor AEFIs following routine immunization vaccines is being done through AEFI registers at facility / block / planning unit level. Further, aggregate numbers are entered into the HMIS through the Monthly Progress Report of the PHCs. During the COVID-19 vaccination campaigns, CoWIN-SAFE-VAC was used to report minor, serious and severe AEFIs by vaccinators at the session site and DIOs at the district level.

It is proposed to set up a system similar to CoWIN for routine immunization which will have features to allow electronic reporting of all types of AEFIs by vaccinators, medical officers, DIOs and other medical/paramedical staff. Improving reporting of minor AEFIs through software-based reporting and management solutions provides automated, easy and early analysis of available information for identification of programme errors and signal detection.

4.11 Steps to Encourage Reporting from all Stakeholders

Staff should be encouraged to inform/notify AEFIs without fear of penalty. Reporting can be enhanced by:

- Sensitization and periodic refresher trainings
- Regular feedback to Medical Officers and health workers about the investigation status and causality of the AEFIs reported by them as well as any corrective actions taken/required
- Ensuring there are enough support available at all levels
- Confidence building of the staff reporting AEFIs
- Commendation/appreciation to the districts/health facilities for better reporting both in terms of quality and quantity

Private sector reporting of AEFIs needs to be encouraged through sensitization and engagement of IAP & IMA chapters at district levels and state levels.

The various channels and frequency of reporting AEFI cases are listed in Table 4.2.

Table 4.2: Channels and Frequency of Reporting AEFI Cases

Reporting Channel	Frequency	Categories of vaccine reactions to be reported
AEFI reporting and investigation formats (CRF & CIF)	Immediate notification and reporting	Serious and Severe
AEFI Registers	Weekly	Serious, Severe and Minor
SAFE-VAC (Co-WIN SAFE-VAC for COVID-19 vaccination)	Immediate	Serious, Severe and Minor
Monthly Progress Report (HMIS)	Monthly	Serious, Severe and Minor

Summary

- Any health care provider (public or private), ICDS worker, ASHA, community lay person can notify AEFIs to the medical officer of the PHC or the district health authority/ immunization officer by quickest means of communication e.g. telephone, WhatsApp, Email, SMS, messenger etc.
- All AEFIs following use of any licensed vaccines (UIP and non-UIP) given in both government and private sector in India should be reported through the AEFI surveillance system.
- Serious or severe AEFI cases should be provided immediate medical care followed by initiation of the process of reporting as per guidelines.
- Minor, serious and severe AEFIs should be recorded in AEFI registers and their numbers reported in HMIS.
- The process of notification to the medical officer or the DIO begins when an AEFI case is informed to any frontline worker or health staff or doctor (in private or public sector).
- The Case Reporting Form (CRF) captures basic minimal information pertaining to the patient, event, vaccine, diluent and reporter.
- CRF is filled by MO in-charge and sent to DIO within 24 hrs after notification. DIO has another 24 hrs to verify the case and submit the CRF into SAFE-VAC. The case ID will be generated by SAFE-VAC.
- The DIO will plan and lead the investigation of an AEFI case with the support of members of District AEFI Committee. DIO must submit Case Investigation Form (CIF) within 21 days of notification.
- A private practitioner or health care facility or ADR Monitoring centres can inform / notify an AEFI case to concerned government MO / DIO. Thereafter, the case should be investigated by the district health authorities.
- Separate CRFs and CIFs need to be filled for each case of a cluster. A summary of the investigations and a single linelist with details of each case of the cluster should also be prepared for a better understanding of the cause of the events.
- Minor AEFIs are currently reported through AEFI registers and monthly progress reports. The data should be analysed periodically for inference and necessary action.
- It is proposed to enable routine immunization software management systems for electronic reporting of minor AEFIs (in addition to serious and severe AEFIs) by vaccinators and other health staff.

5 AEFI Investigation

5.1 Why AEFI Should be Investigated?

The ultimate goal of investigating a reported AEFI is to make a valid diagnosis and establish if the event has any relation to immunization. This is based on a review of the chronology of events, circumstantial evidences, cold chain status, detailed medical history, epidemiological and other evidences such as laboratory investigations. This will, in turn help in causality assessment and plan the appropriate action. An investigation should identify any immunization-related errors because these are preventable. At the same time, recognition of co-incidental events and their communication with the stakeholders is important to maintain public confidence in the immunization programme. The objectives of investigating an AEFI case are to:

- Confirm/refute the reported diagnosis or establish a valid diagnosis for the reported event.
- Document the outcome of the event.
- Identify details of implicated vaccine(s) administered and determine the time interval between administration of the vaccine and the onset of the event.
- Examine operational aspects of the immunization programme or vaccine administration. This should be done even if an event seems to be vaccine product related or coincidental, since immunization-related errors could have triggered or increased its severity.
- Determine whether a reported event was a single incident or one of a cluster. For a cluster of events, the protocol for investigation of clusters should be followed.
- Determine whether similar events occurred or are occurring in individuals not immunized with the implicated vaccine.

5.2 Which AEFI Should be Investigated?

All reported severe and serious cases are to be investigated.

- As per WHO, serious events of known or unknown cause include the following:
  - » Death or life-threatening cases
  - » In-patient hospitalization or prolongation of existing hospitalization
  - » Persistent or significant disability/incapacity, requiring intervention to prevent permanent impairment or damage
  - » Congenital anomaly/birth defect
  - » Cluster of AEFIs (including minor AEFI)
  - » Events causing significant parental or public concern
- Suspected immunization error
- Signals and events of special interest or events associated with newly introduced vaccines
- Significant events of unexplained nature or cause
- Events included in the list of reportable AEFIs (refer to reportable AEFIs in Chapter 4)

5.3 Steps in Investigating AEFIs

The following are the steps in investigating an AEFI:

1. The MO visits the case for confirmation and fills Case Reporting Form (CRF). In case the patient is hospitalised, the medical officer may contact the treating physician telephonically. CRF is sent to DIO within 24 hours of notification.
2. DIO evaluates completed CRF and submits it on SAFE-VAC immediately but not later than 48 hours of notification.
3. The DIO initiates the process of planning of investigations as soon as the CRF is received and it is verified that the case is serious/severe. If required, especially in clusters or cases attracting community concern, he consults the district AEFI committee for support in investigations.
4. Findings during investigation are recorded in the Case Investigation Form (CIF). The filled CIF is submitted on SAFE-VAC within the stipulated timeline. Appropriate action at local level is taken by DIO as advised by District AEFI Committee.
5. At the time of submission of CIF, if all investigations are complete, all relevant expected records are available and outcome of the patient is known, the submitted CIF can be considered final. In a few cases in which the outcome is not final or some more pending documents are expected at the time of submission of the CIF, the pending records can be uploaded in SAFE-VAC later.
6. The CRF, CIF and all available case records should be uploaded in SAFE-VAC before 21 days of notification. If the district AEFI committee is not held within 21 days of notification, the CIF can be uploaded in SAFE-VAC if all other sections are complete without district AEFI committee meeting details, opinion and signatures. Once the meeting is conducted, the updated CIF with the diagnosis and signatures of the district AEFI committee should be uploaded in the "additional records" folder of the case in the SAFE-VAC.
7. It is important for the investigation to be conducted in a thorough and timely manner so that the state AEFI committee can decide on the causality of the AEFI and follow-up action can be taken.

5.3.1 Initial Response of the Health Worker to the AEFI

As soon as any serious or severe adverse event is recognized, the health worker should communicate the same to the medical officer in-charge of the Primary Health Centre (PHC) and initiate necessary steps for the management of the case, including referral to the nearest health facility, if required. The health worker should also assure the parents or guardians that an enquiry is being initiated to determine the cause for the same. The basic information about the event, as well as the demographic details should be gathered by health worker and shared with the Medical Officer on his/ her visit.

All used vaccine vials should be preserved under proper cold chain conditions at the nearest cold chain point for 48 hours or till the next session. In case any AEFI is reported, then these vials are not discarded until further directions from the higher level.

5.3.2 Confirming and Reporting the AEFI

On receiving information of an AEFI from the health worker or through print or electronic media, the MO should ensure appropriate treatment to the case and if required, the patient may be referred to a hospital for treatment. Then he should gather more details related to the event. He should identify the session in which the case was vaccinated and obtain all immunization records of the session including the due list cum tally sheet. He should visit and examine the vaccine recipient, and interview the family. He should collect detailed data about the patient, vaccine/s administered, immunization session in question, manufacturer and batch numbers of vaccines used in that session, etc. He should complete sections A, B, C and D of the CRF after framing a provisional diagnosis (which may not be accurate at this stage) and submit the CRF to the DIO within 24 hours of case notification. In section D of the CRF, a clear sequence of onset of signs/symptoms and clinical manifestations should be described along with initial diagnosis.

5.3.3 Decision on Investigation by the District

On receiving the Case Reporting Form (CRF) from the medical officer, the DIO should verify the details in sections A, B, C and D and fill the section E of CRF. DIO should confirm date of onset of the event, vaccine details and make sure that the entries in the CRF are clear and complete.

The DIO will then start the process of entering data from the CRF through SAFE-VAC. As he starts the process, the software will generate a case ID (EPID Number) which the DIO will write on the CRF. After data entry, the handwritten and signed CRF with the unique case ID is scanned and uploaded on SAFE-VAC. Through SAFE-VAC, the case will be reported at state and national level simultaneously. The details of the case should also be included in the monthly routine report for HMIS and the AEFI register at the PHC. The CRF is then filled for records.

The EPID Number generated by SAFE-VAC will be in the following format: IND (AEFI) - ST - DIS - YR - NUM (similar to EPID numbers for AFP cases) where:

- IND (AEFI) indicates country code (India) and the condition (AEFI)
- ST indicates the state code (always two alphabets)
- DIS indicates the district code (always three alphabets)
- YR represents the year of event onset (e.g. 14 for 2014) and
- NUM denotes the serial number of the AEFI detected in the district in that year

Therefore, IND (AEFI)-UP-GZA-19-001 will be the code of the first AEFI case (001) investigated in Uttar Pradesh (UP) in Ghaziabad district (GZA) in 2019.

Once a decision is taken to investigate the serious or severe case, DIO will initiate appropriate actions such as informing the district AEFI committee members, deciding on date and time of investigation, etc. In case of death, copies of the CRF should be sent to the team conducting autopsy & other stakeholders. He should contact a member of the district AEFI Committee, preferably a paediatrician, in case of AEFIs in children, for conducting verbal autopsy.

Only if considered appropriate, the implicated vaccine vial and /or any other logistic samples (e.g. auto disable syringes) should be collected and dispatched to appropriate laboratories with Laboratory Request Form (**Annexure 13**).

5.3.4 Investigation of the Event and Collection of Desired Information

AEFI case investigation should be conducted by a team of investigators consisting of members of the District AEFI Committee. The investigating team should preferably include a paediatrician. The investigating team will be co-ordinated by the DIO. The medical officer of the PHC and health worker who conducted the immunization session related to AEFI should support the investigation by providing background information of the case and vaccination records, session site records, etc. During the investigation, information should be collected regarding the pre-vaccination health status, previous and current treatment taken and hospital records, and verbal autopsy and post-mortem details (if conducted) in case of death. Verbal autopsy is to be done in all death cases, even if a post-mortem examination has been done, except in those hospitalised cases in which cause of death is certain. The drug inspector should be involved in the investigation of the AEFI case whenever there is suspicion of vaccine quality defect and in case of cluster of AEFI cases.

Using the Case Investigation Form (CIF) as a guide, the DIO should collect data on the health status of the vaccinee, events that followed vaccination, immunization services, etc. It would also be very helpful to obtain all available medical files (or clinical records) of the vaccinee to check details about the event. Obtain any additional details missing in the CRF and CIF and identify any other cases that need to be included in the investigation.

In a meeting of the District AEFI Committee, the members should discuss and synthesize the information gathered during the investigation of the event from various sources, the observations made and the documents collected, and arrive at a provisional diagnosis. The CIF should be completed and signed by the members. The completed CIF should be entered in SAFE-VAC and the scan of the CIF with the supporting documents including the patient's treatment received, investigations, discharge slip, post-mortem findings (for deaths) and/or verbal autopsy, any other supporting documents should be uploaded as soon as possible.

The District AEFI committee and DIO should also try to identify the possible cause, especially the events suggestive of immunization errors and the possible causes or practices. They should take appropriate action based on the problems and issues identified during the investigation and/or the feedback from the State (and national) level.

To understand the steps and decision-making aspects of AEFI investigations, e-learning courses on AEFI investigation developed by the WHO are available at the following links:

- https://openwho.org/courses/vaccine-safety-basics
- http://investigation.gvsi-aefi-tools.org/investigation/index.html#step

While Conducting an AEFI Case Investigation, be prepared for

- Obtaining details of session site - The due list cum tally sheet, vaccine details and stock registers related to the session should be ready before the visit of the investigating team.
- Visiting the immunization site, vaccine storage points, residence and neighbourhood of the patient and the treatment centre(s).
- Interviewing the patient, parents or guardian, the treating health staff, the staff who provided immunization, and people in the community and collect relevant information.

Steps in Investigating AEFIs

1. **Confirm information in CRF**
2. **Investigate and collect data**
   - » About the patient
   - » About the event
   - » About the suspected vaccine(s)
   - » About other people of the area/ community
3. **Assess the immunization service by**
   - » Making enquiries
   - » Observing the service in action
4. **Specimen collection when applicable**
   - » From patient
   - » Vaccine and logistics
5. **Conclude Investigation**

Possible Sources of Information in AEFI Investigation

- Interaction with family/case
- Visit to hospital/clinic/ward
- Interaction with treating physician/ health care provider/clinician
- Visit to immunization site
- Interaction with the vaccinator (health worker), other frontline workers at the session site
- Review of vaccine storage and handling practices
- Visit to community and other vaccination sites in the block/district, if needed
- Review of investigation reports e.g. blood, urine, CSF etc.

Step 1: Confirm Information in Report

- Obtain patient's medical file (or other clinical records, lab investigation reports, etc.)
- Check details about patient and event
- Confirm information in the CIF
- Particularly verify the time sequence of vaccination and the reported event
- Obtain any details missing from AEFI reporting / investigation forms
- Identify any other cases that need to be included in the investigation

Step 2: Investigate and Collect Data

Step 2a: Investigate and collect data about the PATIENT

Review patient records for:

- Immunization history
- Previous medical history, including prior history of similar reaction or other allergies
- Family history of similar events

Step 2b: Investigate and collect data about the EVENT

- History of the event in chronological order to explore the underlying factors, if any
- Detailed clinical description including condition of the patient before vaccination, time interval between vaccination and onset of symptoms, sequence of clinical manifestations and the response to treatment
- Results of relevant laboratory tests and other investigations (e.g. X- ray, ECG, etc.) conducted
- Details of treatment and outcome

Step 2c: Investigate and collect data about the SUSPECTED VACCINE(S)

- Shipping conditions from manufacturer to the last major storage point
- Storage point conditions (refrigerator), documentation and transport to vaccination site
- Vaccine handling at the site - cold boxes, condition of ice packs and duration of exposure to ambient temperature
- The condition of vaccine vial monitor
- Time and date of opening the vial
- Date and time of vaccinations during the immunization session e.g. whether the case was vaccinated at the beginning /end of session
- Condition of vaccine labels and date of previous use, in case of reuse of previously opened vaccine vials

Step 2d: Investigate and collect data about OTHER PERSONS

- Whether others in the community had similar illnesses - use a case definition, categorize cases and determine the vaccination status of the affected persons, if any
- If possible, try to obtain details of other beneficiaries (obtained from due list cum tally sheet) who received the vaccine from
  - » the same distribution point
  - » the same centre
  - » the same day
  - » the same vial

Step 3: Assess the immunization Services

Step 3a: Assess the immunization service by making enquiries

- Dosage, person, site and technique
- Vaccine storage, distribution and disposal
- Reconstitution procedure
- Time between reconstitution and administration
- Number/ type of immunizations and other medications given (e.g. Vit A) in the session
- Staff training status

Step 3b: Assess the service by observing it in action

- How vaccines are placed in the cold chain
- Whether other drugs are also stored with vaccines/diluents
- Whether any vials have lost their labels
- Batch numbers and expiry dates
- If any of the opened vials look contaminated
- Directly observe the immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes; disposal of opened vials) - if possible
- Whether Open Vial Policy is followed as per guidelines

Sense the ambience of the immunization session (including the interaction of the health worker with beneficiaries) and try to assess if it is organized properly and in a child friendly manner.

Step 4: Specimen collection

Step 4a: Specimen collection: Patient

A guide for the treating physician to collect the following specimens which will help in completion of investigation, Table 5.1 (see details in Chapter 7).

Table 5.1: Specimen Collection-Patient

Event	Specimen from the Patient
Severe local reaction	Blood
Abscess	Swab, Blood, Pus
Lymphadenitis	Blood, FNAC
CNS symptoms with paralysis/ no paralysis	Cerebrospinal fluid, blood and stool (Ensure that AFP reporting has been done for all cases with paralysis)
Anaphylaxis	Blood
Toxic Shock Syndrome	Blood
Death	Post-mortem tissue specimens

Step 4b: Specimen collection: Vaccine

- **Testing vaccine quality is RARELY needed.** It should be done only on clear suspicion, and NOT as a routine, and never before a working hypothesis has been formulated.
- **The DIO will consult the state immunization officer and convey the opinion of the SIO to the district AEFI committee, regarding sending the vaccine samples for testing to CDL, Kasauli. Only then, the district AEFI committee should take a decision on sample testing.**

Following tests may confirm/rule out the working hypothesis

- » Sterility (vaccine and/or injection equipment)
- » Chemical composition (analytical)
- » Preservatives, adjuvant level etc. (e.g., aluminium content)
- » Abnormal components (e.g., suspect drug instead of vaccine)
- » Biological tests (abnormal toxicity)

Some of the tests listed above can only be done in highly specialised laboratories outside the country and requires a lot of specific processes. Testing for abnormal components such as drugs other than the diluent in the vaccine is an example.

Step 5: Concluding Investigation

- Review epidemiological, clinical and laboratory findings
- Formulate a likely valid diagnosis
- Reach a provisional conclusion on the cause
- Complete the CIF

The DIO should ensure that:

- the investigation of the case is completed
- the documents are reviewed for establishing the sequence of events leading to a likely diagnosis of the case by the district AEFI committee
- the completed CIF and other documents are submitted on SAFE-VAC within 21 days of case notification for sharing with the State Immunization Officer and Immunization Division / AEFI Secretariat

Copies of the following documents are expected to be uploaded in SAFE-VAC along with the CIFs:

1. Hospital Records
2. Results of any pathology/microbiology (blood, CSF, urine, etc.)/radiology tests
3. Doctor's prescription/treatment record for this AEFI
4. Doctor's prescription/treatment record for other illness
5. Report of laboratory test of vaccine/diluent (if sent for testing)
6. Result of laboratory test of syringes/other drugs
7. In case of death:
   - » Death certificate (if available)
   - » Completed verbal autopsy form
   - » Post-mortem reports - preliminary and final, with cause of death report (if conducted)
8. Any other relevant document

5.3.5 Investigation of AEFIs following COVID-19 vaccinations

Unlike the routine immunization, COVID-19 vaccination was carried out for a new disease prevailing in epidemic conditions and was administered to adult population. This necessitated several changes in the AEFI reporting and surveillance.

Changes in the Case Investigation Form - In view of the additional information required to be collected during the case investigation of AEFI following COVID-19 vaccinations, the following elements have been added to the case investigation form:

(a) Relevant patient history related to COVID-19 infection/contact with COVID-19 positive person

(b) History related to any pre-existing illness/comorbidity/congenital disorder/treatment

Based on the epidemiological situation, some additional investigations may be necessary or specific information in the form of observations or test results may be required to be collected related to certain vaccines or disease for which the vaccine has been used. An example is the guidance to ensure RTPCR/RAT tests for COVID-19 infection are conducted in all deaths and hospitalizations reported as AEFIs following COVID-19 vaccines.

5.3.6 Investigation of Reported AEFI Deaths

A field investigation of a reported AEFI death should be conducted without any delay as it is a serious event, can cause significant community concern and affect vaccine confidence. The CRF should be uploaded through SAFE-VAC. It is recommended that investigation of a reported AEFI death should be carried out by a team comprising clinical, laboratory and forensic experts at the earliest possible. Investigation of a reported AEFI death is discussed separately in chapter 6.

DEATH

- A post-mortem within 72 hours provides the best information
- The post-mortem should be conducted in a medical college or District Hospital (where no medical college is available) with a panel consisting of atleast a Forensic Medicine specialist, Pathologist and a Paediatrician/ Medical specialist.
- Viscera should be sent for histopathological examination (HPE) and toxicology as per state guidelines and videography should also be done.
- If post-mortem is not possible, try to obtain biological specimens from the dead body for lab tests
- It is essential to carry out a focussed verbal autopsy (by trained health personnel) even in cases in which post-mortem has been conducted.

5.3.7 Investigating AEFI Clusters[33,34]

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place, vaccinator or vaccine administered. The exact nature of the relationship between the adverse events such as duration of "time", proximity of "place" will differ by the nature of the events and the circumstances in which they occur. A cluster may occur within the same district or geographical unit, or be associated with the same vaccine, same batch number administered or same vaccinator. Cluster investigations begin by establishing the case

33. https://itsu.org.in/wp-content/uploads/2022/10/SPECIAL-INVESTIGATION-PROTOCOL.pdf;
34. https://itsu.org.in/adverse-event-following-immunization-resource-materials-ri-3/

definition and identifying all cases that meet the case definition (Table 5.2). The DIO should then take two actions-

1. **Identify the common cases (the cluster cases) including details of when, where and which vaccines were given, by collecting and recording:**
   - Detailed data on each patient
   - Programme-related data (storage and handling of vaccines, etc.)
   - Information regarding immunization practices of health workers for preparation, handling, reconstitution and administration of vaccines

2. **Identify any common exposures among the cases, such as:**
   - Vaccine(s) administered (name, lot number, etc.)
   - Same vaccinator
   - Same immunization session
   - Common recipient characteristics such as age, nutritional status, same family etc
   - Data on other people in the area who may not be exposed to the vaccine but may have similar signs and symptoms

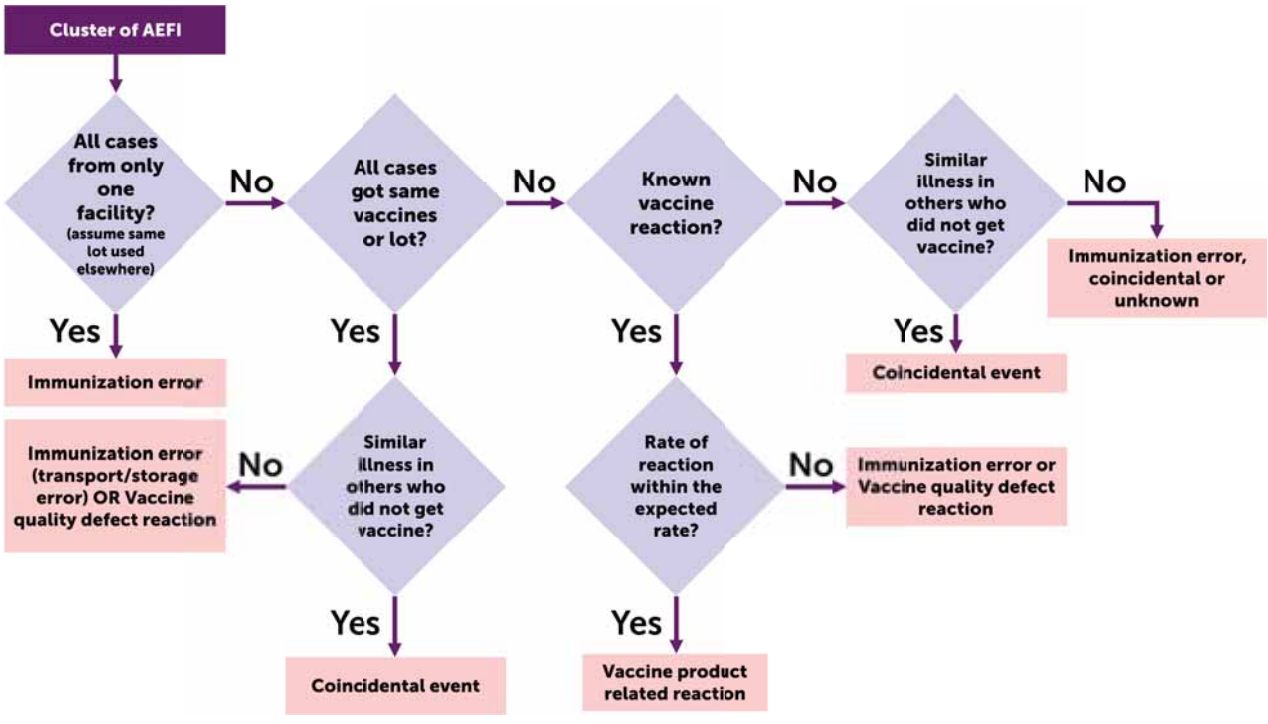
Table 5.2: Characteristics of AEFI Cases of a Cluster

Cause–Specific AEFI	Cluster Characteristics (Indicating Probable Cause)
Vaccine product related reaction	• If all cases received the same vaccine and there are no similar cases in the community. • If an increased frequency of events is reported from multiple settings.
Vaccine quality defect-related	• If all cases received the same vaccine or lot. • If an increased frequency of events is reported from multiple settings.
Immunization error-related	• If all cases received vaccines from the same health worker/ facility and there are no other cases.
Coincidental	• If cases also include people from the same area in the same age group but were not vaccinated
Immunization anxiety-related reaction (Immunization triggered stress response)	• Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during mass vaccination campaign

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually, the key considerations will be to investigate the possibility that an immunization error, or much less commonly, a vaccine quality defect, may have occurred. Therefore, detailed information regarding the vaccine, time and place of administration must be collected. For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-

related reaction. Knowledge of the vaccine reaction rates and background rates of reported events is essential for assessing a cluster in terms of the strength of the signal it may provide. Identification of causes of an AEFI cluster is given in Figure 5.1.

Figure 5.1: Identifying Causes of an AEFI Cluster



Case Studies (Cluster Cases)

(a) In 2018 in state A, four deaths were reported from a session site within 12 hours of vaccination. All the four cases received either MR/ JE/ both MR and JE vaccine. All cases presented with fever, diarrhoea and vomiting within 2 hours following vaccination. Only these four children had received MR and/or JE vaccines in this session. Other children vaccinated with pentavalent, OPV, rotavirus vaccine, IPV and PCV during the same immunisation session had no complaints. Investigations established the diagnosis of toxic shock syndrome in the affected children. On investigation, lapses in the cold chain maintenance at the session site were identified - the MR and JE vaccines were used beyond the recommended time since reconstitution and not always kept on ice packs during the session. Also, the vaccinator had used a single syringe for reconstituting multiple vaccine vials in the same session.

Valid diagnosis: Toxic shock syndrome

Cause: Incorrect vaccine handling after reconstitution

(b) In 2019 in state C, three infants died after administration of JE vaccine. All of them developed similar symptoms within half an hour following immunization. These included hypotonia, difficult breathing and unconsciousness. Only the three infants who received JE vaccine developed symptoms. Other children who received different vaccines in the same immunisation session had no complaints. On investigation, it was found that

other injections, including a muscle relaxant, were kept in the refrigerator along with the vaccines. No testing of the used vaccine vial could be done.

Valid diagnosis: Muscle paralysis including that of respiratory muscles

Cause: Probable erroneous reconstitution of JE vaccine with a muscle relaxant

Additional resources

WHO resources on AEFI investigation are available at:

- https://investigation.gvsi-aefi-tools.org/#step-1
- https://cdn.who.int › pvg › new-aide-memoire-aefi

Summary

- Investigation of an AEFI should be timely, comprehensive and methodical.
- Laboratory investigation(s) of vaccine and other logistics should be conducted only if indicated and necessary.
- It is recommended to store used vaccine vials and syringes, biological samples, etc. in proper conditions, in case they are needed later for laboratory investigations.
- The DIO should ensure that the investigation of the case is initiated as soon as the AEFI is reported and completed and documents submitted on SAFE-VAC within 21 days of case notification.
- Verbal autopsy is to be done in all death cases except in those hospitalized cases in which treatment records are complete with diagnosis and cause of death.
- Investigation of clusters should be immediate, detailed and with proper determination of probable causality as many are affected, creates anxiety in the community and attracts media attention which may be detrimental to trust in vaccines.
- The completeness and quality of AEFI investigations are critical for characterization of the event and establishing its cause.
- Certain changes in investigations and collection of specific additional information may be required if a new vaccine is introduced for a new disease.

6 Investigation of Reported Deaths Following Vaccination

Vaccines are among the safest medical products in use today. However, deaths that are temporally associated with vaccination are often reported. Reported deaths following vaccination have a negative impact on vaccination program. Thus, whenever a death is reported following vaccination, it is important to investigate and assess whether it was related to the vaccination or not. In most of the reported deaths, the reason for death is coincidental and not causally associated with vaccine. Deaths having consistent causal association with vaccines are very rare and may be related to vaccine product (e.g. anaphylaxis, viscerotropic disease), vaccine quality defect (e.g. an incompletely attenuated live vaccine agent), or immunization error related (e.g. vaccine vial contamination resulting in toxic shock syndrome).

Sometimes, a death temporally related to vaccination may occur suddenly, without prior history of any illness/ hospitalization, and often at home. Such a death especially that of a child, is traumatic to a parent/ family and raises questions regarding vaccine safety. Investigation of unexplained deaths following immunization is an issue of great importance with regard to the immunization programme, as proper causality assessment would enable differentiation of vaccine-related deaths from deaths due to other causes.

Many cases of sudden unexplained deaths may be due to a previously undiagnosed illness. In rare instances, death may be caused by accidental injury or environmental factors (e.g. hypothermia). In recent times deaths from genetic, metabolic or cardiac disorders that were previously unknown have come to light. It is important to identify these in order to protect other children and maintain trust in vaccines.

Since many conditions may lead to a sudden and unexpected death, a detailed investigation is needed to evaluate these cases reported as AEFIs. This should include a thorough history investigation of circumstances of death, medical examination, post-mortem examination and interviews with doctors, ANM, ASHA and other people involved with the family during the few days preceding or around the death. It is critical to collect and review all available medical records of any previous illnesses the child might have had and of the current event reported as an AEFI. OPD slips, in-patient records, discharge summary, reports of investigations conducted and death summary, if available, are valuable records to arrive at a possible cause of death. The doctors conducting the post-mortem may also be consulted for information.

The investigations of AEFI deaths are multidisciplinary and final interpretation of results would require corroboration with a detailed account of events that may be forgotten unless documented relatively soon after the incident. Delay in investigation may lead to loss of crucial evidence. In order to find evidence for causes of death such as trauma, falling from

the crib/ cot or parents accidentally rolling over the baby during sleep, etc., the investigator should examine the site of death. If the body has not been moved, a photograph may be taken for the purpose of documentation. Separate verbal autopsy forms for recording the narrative and circumstances around AEFI deaths in children and adults have been developed to help in arriving at a diagnosis and causality regarding the AEFI deaths.

6.1 Verbal Autopsy

The verbal autopsy should be conducted by a trained medical officer (DIO) using the verbal autopsy form that has been customized for investigation of deaths following vaccination. It is desirable that a paediatrician/physician should assist the DIO in administering the verbal autopsy form. A paediatrician/physician has the expertise to ask in-depth questions to verify or arrive at a clinical diagnosis. The verbal autopsy should be conducted in privacy with empathy towards the family of the deceased. Leading questions should be avoided.

Verbal autopsy needs to be conducted/administered in all death cases, irrespective of whether a post-mortem has been conducted or not. The objective of conducting a verbal autopsy is to collect detailed information regarding the terminal event, especially, in cases brought dead to health facility, home deaths (or non-hospitalized cases), cases with insufficient medical records regarding the event or deaths in which clinical diagnosis is not possible based on available evidence. In a case where the cause of death can be ascertained from medical records, a verbal autopsy may inform about the additional risk factors and chronology of the events that led to death. Therefore, verbal autopsy form need to be mandatorily filled in all cases of deaths including deaths after hospitalisation. For an informed causality assessment, in case of deaths following hospitalisation, the copies of all related documents are expected to be uploaded in SAFE-VAC along with the CIF. Please refer to Step 5, under section 5.3.4 for detailed list of documents.

6.1.1 Verbal Autopsy Form (Children <18 years)

Use of the verbal autopsy form for children facilitates recording the events prior to death, description of the death scene and sequence of events leading to death (**Annexure 10**). Some of the salient details that are recorded in the verbal autopsy form include:

- **Personal information:** Name of the child, age (date of birth), sex of the child, name of the parents, caregiver (other than parents, if any), grandparents and other family members if living in the same house etc., address
- **Details about event:** Date and time of death, location of death (includes hospital), events that happened before death in chronological order
- **Immunization details:** Site of last vaccination given, route of vaccination, location of vaccination session, name of person who gave the vaccine, date and time of vaccination, history of any local reaction at the site of vaccination, history of any adverse effect during past immunization, the status of other children vaccinated in the same session site, etc.

Overview of the event leading to death: A history related to the incident must be provided - who was involved, what happened, where, and when the incident occurred. The investigation

team must visit the site of incident to document and obtain more information. A detailed history that includes a verbatim description of events starting from 24 hours prior (or earlier if indicated) and up to the occurrence of events and declaration of death is essential to understand the cause of death. Hence, a host of other common causes need to be excluded. Review of the environment where the event happened, family structure, other stressors in family like family discord, alcohol/drug abuse among parents/other family members, health of other children, presence of over-crowding/unhygienic conditions, etc. contribute significantly in forming an overall impression and point towards possible cause of death. This impression must be included in the summary provided by the investigator at the end of the verbal autopsy form.

6.1.2 Verbal Autopsy Form (Adults)

Verbal Autopsy form for adults was developed to capture relevant medical history of the beneficiaries. It is to be filled for all death cases using the Verbal Autopsy form for adults (**Annexure 11**). Some of the relevant sections included in the verbal autopsy form are:

- Past history including any pre-existing illness, history of past hospitalization, medication, investigations, etc.
- Information regarding the co-morbid conditions and long-term medication use
- Relevant Obstetrics and Gynaecology history among women
- Information regarding relevant systemic involvement such as respiratory system, cardiovascular system, gastrointestinal system, central nervous system, genitourinary system
- Relevant information regarding COVID-19 infection/post Covid vaccination
- Details of any treatment or medication prior to event of death
- Relevant risk factors such as smoking, alcohol, drug abuse, occupation, etc.

6.2 Guidance on Conducting Post-mortem

It is desirable that all cases of deaths following vaccination should be converted into medicolegal cases (MLC). Cases of sudden death, in particular, raise suspicions and require further exploration, even if the medical history suggests a natural cause. Classifying deaths that occur after vaccination as MLC would help in assessing those cases in which cause of death cannot be ascertained by a certified doctor. It is crucial to avoid issuing death certificate in such cases and report the matter to the police as an MLC. Once the case is converted into an MLC case, the family's consent is not necessary for conducting a post-mortem examination. This procedure is vital for determining the actual cause of death and to rule out any potential legal or forensic implications.

Whenever feasible, a post-mortem examination and related laboratory investigations should be conducted for the AEFI deaths. The regular post-mortem conducted in districts are not oriented towards identifying pathological causes of death. Therefore, guidelines for conducting post-mortem in AEFI deaths have been developed and the format is attached in the **Annexure 12**.

It is recommended that a post-mortem in an AEFI death case should be performed as soon as possible to avoid tissue damage, development of post-mortem artefacts and lysis of the

internal organs, which can alter diagnosis. The DIO should ensure that a detailed patient's history is included in the post-mortem form that is submitted to the team (post-mortem surgeon/ pathologist/ forensic specialist) conducting the post-mortem. The DIO should ensure the following for conducting post-mortem in AEFI cases:

- Identify a medical college in the district or in the neighbouring district where a post-mortem can be conducted. If this is not possible, the post-mortem must be conducted in the district hospital.
- Post-mortem should be conducted by a team with a forensic medicine expert or pathologist.
- If not feasible (due to any delay in transportation/ notification), post-mortem should be conducted by any doctor but in consultation/supervision of forensic expert or pathologist.
- Make arrangements for videography (or photography) of the post-mortem beforehand (for external as well as internal examination).

When a death is reported:

- The health worker/ medical officer should inform the District Immunization officer (DIO) about AEFI death as soon as possible and before the body of the deceased is disposed of.
- The DIO should inform the police on priority to make it a medicolegal case.
- All efforts should be made to convince the parents/family/guardian regarding advantages of doing a post-mortem examination in an AEFI death.
- Approval from family makes the process smoother for police as well as doctors.
- Experts from the departments of forensic medicine or pathology of the local medical college identified for conducting the post-mortem should be informed immediately. Formats for recording additional information should be shared with them beforehand.
- Arrange for transfer of body to the medical college/district hospital.

While conducting post-mortem:

- The process of conducting a post-mortem after an AEFI should typically begin with an examination of external findings, which includes noting details such as the age, sex, height, weight, and overall condition of the deceased. Subsequently, the internal examination is carried out. In case of infants, the examination involves measuring the length of the body and the head circumference (Table 6.1).

Table 6.1: Conducting Post-mortem- External and Internal Examination

External Examination	Internal Examination
External examination involves the examination of following: • Clothes • Stains of mud, blood, urine, stools etc • Identity or identification marks • Body orifices • Finger, toe-nails • Injuries/ surgical interventions • Rigor mortis • Post-mortem staining • Decomposition/ other changes	Internal examination of three major cavities: • Skull/ Cranium • Thorax • Abdomen

- For histopathology, preserve the organ as a whole in 10% formalin solution. Samples for histopathology should be sent to the district hospital or department of pathology of the medical college for analysis through the police. The police may be guided to send the sample to Department of Pathology of the identified medical college.
- Blood for microbiological studies should be preserved in sterile test tubes and stored at 4°C. This should be sent to microbiology department of the identified medical college through the police.
- While sending the samples, provide the full post-mortem report or at least a note as to what is being suspected and for what the sample is to be analysed.
- In suspected cases of poisoning, the viscera/gastric contents should be preserved in a saturated solution of common salt and sent to Forensic Science Laboratory (FSL) for toxicological analysis.
- Blood for toxicological analysis should be preserved in NaF (Sodium Fluoride) solution.
- In cases where multiple samples including viscera for toxicology, tissues for histopathology, or blood are preserved, police may be guided regarding the type of samples preserved and where it should be sent for analysis.
- The post-mortem report should clearly mention the opinion regarding the cause of death, estimated time duration between death and post-mortem, pathology (if present) and articles (if preserved).

Follow up for the reports:

- Preliminary post-mortem report is to be sent with the CIF
- If viscera and samples have been sent for histopathological and chemical analysis, follow up should be done for the reports till these are received.
- After this, a final post-mortem report including the above should be uploaded on the SAFE-VAC/ COWIN-SAFE-VAC portal

6.3 Additional Post-mortem Findings to Confirm Cause of Death

- For deaths suspected to be due to anaphylaxis, look carefully for any rashes or small petechial haemorrhages over the skin and also on the surfaces of internal organs. Look for laryngeal oedema or oedema in lungs and collection of fluid in thoracic or abdominal cavities.
- In deaths due to aspiration, look for gastric contents in the distal and terminal bronchi of lungs. Presence of gastric contents only in trachea does not constitute evidence for diagnosis of aspiration.
- In cases of overlaying/ suffocation look for the cardinal signs of asphyxia like deep congestion of organs, oedema of lungs, bluish discoloration of lips and nails.
- Based on special requirements and circumstances, additional specific internal and external examinations may need to be conducted. For example, Thrombosis with Thrombocytopenia Syndrome (TTS) was recognized as a known adverse event following adenovector-based COVID-19 vaccinations. Therefore, it is recommended to look for

presence of thrombus in coronary or pulmonary vessels while conducting post-mortems in such cases.

- In cases where nothing significant that could point to the cause of death is found, the following should be preserved:
  - » Viscera for toxicology in saturated solution of common salt
  - » All the organs (lungs, liver, spleen, kidney, brain tissue) should be preserved in formalin and sent for histopathology
  - » Blood in sodium fluoride solution
  - » Blood in sterile test tubes for microbiological investigation to be sent at 4 degrees Celsius.
  - » During the examination of a pregnant woman, assess the size of the uterus and foetus to determine the gestational period. Check for indications of potential miscarriage or haemorrhage, depending on the pregnancy stage. Also, consider the patient's medical history, including any past abortions or poor obstetric history. If necessary, retain foetal tissue for DNA genetic analysis.

6.4 Impact of Quality & Timeliness of Post-mortems on Causality Assessment

The state and national AEFI committees encounter various challenges while carrying out causality assessments of death cases. These challenges include the following:

(a) Delays in obtaining post-mortem and/or histopathology reports
(b) Incomplete or illegible reports
(c) It is not known if the preserved viscera samples have been sent further for histopathology and toxicology
(d) Opinion regarding the cause of death is not available/reserved
(e) Discrepancies in information in CRF, CIF, and post-mortem report.

To mitigate these issues, the state AEFI committee can take several measures. Firstly, they can review and provide feedback on the quality of post-mortem reports to the district to ensure their accuracy. Secondly, with the assistance of the District Immunization Officer (DIO), the forensic expert/pathologist in the state AEFI committee can offer guidance and support to the autopsy surgeon at the district level to ensure adherence to established protocols. Thirdly, including a forensic expert in the district AEFI Committee could prove beneficial.

Efforts should be made to provide timely post-mortem reports. Coordination between the DIO and police department could ensure timely receipt of histopathology reports. These measures can contribute to timely and complete causality assessment of deaths.

Summary

- Whenever a death is reported following vaccination, it is important to investigate and assess whether it was related to the vaccination or not.
- The investigations of AEFI deaths are multidisciplinary and final interpretation of results would require corroboration with a detailed account of events that may be forgotten unless documented relatively soon after the incident.
- Verbal autopsy needs to be conducted/administered in all death cases, irrespective of whether a post-mortem has been conducted or not.
- It is desirable that all cases of deaths following vaccination should be converted into medicolegal cases (MLC).
- Identify a medical college in the district or in the neighbouring district where a post-mortem can be conducted. If this is not possible, the post-mortem must be conducted in the district hospital.
- The post-mortem should be conducted by a panel which should have a post-mortem surgeon/ pathologist/ forensic specialist as well as a paediatrician or physician. Videography of the post-mortem should be done.
- In cases where multiple samples including viscera for toxicology, tissues for histopathology, or blood are preserved, police may be guided regarding the type of samples preserved and where it should be sent for analysis.
- Post-mortem after an AEFI is done not merely to exclude unnatural cause of death, therefore detailed gross and histopathology of all organs is important.
- Efforts should be made to provide timely post-mortem reports, and coordination between the DIO and police department could ensure timely receipt of histopathology reports.

7 Specimen Collection and Handling for AEFI

The following types of samples may be required to be tested during an AEFI investigation:

- Biological samples from the patient and
- Vaccines, diluents and logistics such as syringes (where indicated)

Before collecting a specimen (biological, vaccine, diluent or logistics), it is important to clearly understand the need for it.

Laboratory specimens should be accompanied by supporting documents (Lab Request Form (LRF), CRF, CIF and other relevant documents) mentioning the tests to be conducted on the specimens and any specific additional request for information by the investigators.

7.1 Testing of Biological Specimens

Usually, the decision regarding the testing of biological specimens is taken by the treating physician, depending on the clinical signs and symptoms and differential diagnosis. Based on the type of test to be requested, the treating physician decides which sample is to be taken and where the tests will be conducted. However, to help in determining the cause of the AEFI, the district AEFI Committee/ DIO may recommend certain tests to be conducted in identified government and or accredited private laboratories (approved by the competent authority).

Some national laboratories have been identified to conduct tests to find viral aetiology. In case of adverse events occurring following JE vaccination, the CSF and blood samples may be sent to National Institute Virology in Pune or Gorakhpur. For AEFI following MR vaccination, samples may be sent to NIV, Mumbai. Samples should be properly labelled and appropriately packed and transported, with documents such as LRF, CRF, CIF and other relevant records. These institutes have the capacity to identify whether the virus is vaccine virus or wild virus. Contact details of these institutes are given in Table 7.1.

Table 7.1: Contact Details for National Laboratories

Name of Institute	Address	Email Address & Phone Numbers
National Institute of Virology (NIV) Pune	The Director, ICMR-National Institute of Virology (JE Group), 20/A, Dr. Ambedkar Road, Pune, Maharashtra - 411001	director.niv@icmr.gov.in 020-26006290/ 25906890

ICMR- Regional Medical Research Centre, (Formerly ICMR-NIV, Gorakhpur Unit)	Baba Raghav Das (BRD) Medical College Campus, Gorakhpur, Uttar Pradesh -273013	admn-rmrcgkp@nic.in, admnrmrcgkp@gmail.com 0551-2971007
ICMR-NIV, Mumbai Unit (Formerly Enterovirus Research Centre)	Haffkine Institute Compound, A.D. Marg, Parel, Mumbai-400012	nivmumbaiunit@gmail.com 022-24134130/ 24125309

The Table 7.2 below describes the activities and responsibilities of various personnel involved in biological specimen collection following an AEFI.

Table 7.2: Activities and responsibilities for specimen collection following an AEFI

	Activity	Responsibility
1	Decision to collect sample (samples should be collected as soon as possible)	• Treating physician • District AEFI Committee/ DIO may recommend certain tests
2	Laboratory for sending specimen	• Identified government and accredited private laboratories (approved by competent authority)
3	Funding	• The expenses for activities related to AEFI surveillance, AEFI case management and other AEFI related activities can be made from the available funds under PIP FMR code RCH 4- Immunization – S. No. 32 – SSRE (Surveillance Research Review Evaluation). NIV Pune, NIV Gorakhpur and NIV Mumbai will bear the expenses related to testing of samples for adverse events occurring following JE and MR vaccinations.
4	Reporting of laboratory results / reports	• Laboratories will also send copies of laboratory results to all persons with contact details (complete address with pin code, phone and fax numbers and email address) mentioned in the LRF.

While it is the treating physician's prerogative to decide which tests are needed to confirm the diagnosis or to rule out other diagnosis, Table 7.3 gives a general list of tests and biological samples to be collected for certain expected events which are reported as AEFIs.

Table 7.3: Biological Specimens for Testing Following AEFI

Event	Specimen to be Collected	Tests to be Done
Severe Local Reaction Abscess Lymphadenitis	Blood Pus	Culture FNAC
CNS Symptoms (with paralysis/ no paralysis)	Serum Blood Cerebrospinal fluid (CSF) Stool*	IgM and IgG antibodies for viral pathogens Culture Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other) Enterovirus and viral culture
Anaphylaxis	Serum	Mast cell tryptase Specific IgE
AEFI following COVID-19 vaccination	Nasal swab	RTPCR for COVID-19

*If paralysis follows administration of OPV, stool specimens are important. These are to be collected as per the guidelines for stool collection in AFP case

7.1.1 Post-mortem Specimens in a Death Case Suspected to be due to an AEFI

It is recommended that post-mortem in a death case suspected to be due to an AEFI be performed as soon as possible to avoid tissue damage, development of post-mortem artifacts and lysis of the adrenal glands, which can alter diagnosis.

The DIO should ensure that a detailed patient history is included in the post-mortem form that is submitted to the team (forensic specialist/autopsy surgeon/ pathologist/) conducting the autopsy.

This additional specific information to the post-mortem team will help them look for any underlying disease/pathology in the deceased which may be cause of death or may have contributed to death. Samples for both histopathological and toxicological examinations should be sent to approved/accredited government reference laboratories through investigating police agencies. Samples should be collected and transported to forensic laboratories as early as possible to avoid loss of quality due to decomposition. All samples should be labelled properly with copy of post-mortem report detailing the specific tests required to be conducted on the samples. The post-mortem report should ideally list the cause of death as per the International Classification of Disease (ICD 10) and, if possible, the causative agents/drugs. The important aspects to be considered when conducting a post-mortem in AEFI cases are outlined in **Annexure 12**.

7.2 Testing of Vaccine/ Diluents at CDL Kasauli

All vaccines (and diluents) are tested in CDL, Kasauli, Himachal Pradesh for physical aspects, sterility, abnormal toxicity and biochemical identity. Tests for potency are not conducted in AEFI cases. Results are dispatched to the sender in approximately 30 days.

Laboratory testing for implicated vaccines/diluents/logistics should be requested only on a clear suspicion like cluster of AEFI cases, increase in vaccine reactions, public/community concern to maintain confidence in the quality of vaccine and not as routine, and never before a working hypothesis has been formulated.

7.2.1 Sample Collection

The DIO and drug inspector should be involved in the collection of adequate quantity of implicated vaccine/ diluent samples from the site of occurrence of AEFI and last vaccine storage point and shipping the same in cold chain to CDL Kasauli as early as possible. Form 18 is used by drug inspectors, when they are sending the vaccine /diluent samples to CDL Kasauli. When the DIO is sending the samples to CDL Kasauli, the LRF is used.

Table 7.4 describes the number of vaccine vials/diluents of different vaccine that need to be collected while sending samples to CDL Kasauli. After preparing four sealed sets with equal quantity of vaccine vials/diluents,

1. Send one set to CDL Kasauli.
2. Retain one set at the site of collection (PHC/CHC or district HQ).
3. Retain two sets with the drug inspector.

The desired quantity of vaccines or diluents must be collected from the next available vaccine storage point. If the vaccine is freeze dried, then same quantity of diluents are required along with the vaccine. If the numbers outlined in Table 7.4 are not available at the last vaccine storage point, it is important that the quantity required by the CDL Kasauli must not be compromised.

Table 7.4: Quantity of Implicated Vaccine/Diluents to be Collected

Vaccine	Quantity to be collected		Quantity to be shipped to CDL Kasauli for testing	
	Unused vaccine vials/ ampoule	Unused diluent vials/ampoule	Unused vaccine vials/ ampoules (1/4th of total samples collected)	Unused diluent vials/ampoule (1/4th of total samples collected)
	(A)	(B)	(C)	(D)
DPT group of vaccines (including Pentavalent)	10 doses x 40 vials OR 01 dose x 120 vials	NA NA	10 doses x 10 vials OR 01 dose x 30 vials	NA NA
BCG Vaccine	10 doses x 160 vials 20 doses x 160 vials	160 diluents 160 diluents	10 doses x 40 vials 20 doses x 40 vials	40 diluents 40 diluents

Vaccine	Quantity to be collected		Quantity to be shipped to CDL Kasauli for testing	
	Unused vaccine vials/ ampoule	Unused diluent vials/ampoule	Unused vaccine vials/ ampoules (1/4th of total samples collected)	Unused diluent vials/ampoule (1/4th of total samples collected)
	(A)	(B)	(C)	(D)
Oral Polio Vaccines	20 doses x 40 vials	NA	20 doses x 10 vials	NA
Measles / MMR / MR	01 dose x 80 vials OR 05 doses x 60 vials OR 10 doses x 40 vials	80 diluents 60 diluents 40 diluents	01 dose x 20 vials OR 05 doses x 15 vials OR 10 doses x 10 vials	20 diluents 15 diluents 10 diluents
JE & Hepatitis Vaccines	01 dose x 80 vials OR 05 doses x 60 vials OR 10 doses x 40 vials	80 diluents 60 diluents 40 diluents	01 dose x 20 vials OR 05 doses x 15 vials OR 10 doses x 10 vials	20 diluents 15 diluents 10 diluents
IPV	5 doses x 40 vials OR 10 doses x 40 vials OR 1 dose x 80 vials	NA	5 doses x 10 vials OR 10 doses x 10 vials OR 1 dose x 20 vials	NA
Rabies vaccine	1 dose x 60 vials	60 diluents	1 dose x 15 vials	15 diluents
Rotavirus vaccine (oral)	01 dose x 80 vials OR 2 doses x 80 vials OR 05 doses x 60 vials OR 10 doses x 40 vials	NA	01 dose x 20 vials OR 2 doses x 20 vials OR 05 doses x 15 vials OR 10 doses x 10 vials	NA
Pneumococcal vaccine	4 doses x 60 vials	NA	4 doses x 15 vials	NA
COVID-19 vaccine	10 doses x 8 vials 20 doses x 5 vials	NA	10 doses x 8 vials 20 doses x 5 vials	NA

The Table 7.5 describes the activities and responsibilities of various personnel involved in specimen collection following an AEFI.

Table 7.5: Collection of Samples of Vaccine Vials/Diluents/Syringes Following an AEFI

Activity	Responsibility
Decision to collect samples	District AEFI committee that includes local Drug Inspector. If required consult state AEFI committee
Collection and sending samples	Drug inspector and DIO
Decision on sample types for collection	Based on recommendations of the District AEFI committee. The Drug Inspector may also collect additional samples as appropriate.
Samples: Packaging & cold chain	Drug Inspector and DIO
Sealing of specimen using "official lac seal"	Preferably by Drug Inspector; in case the drug inspector's seal is not available, then use the CMO's seal.
Transportation of samples to laboratories	Preferably DIO and / or Drug Inspector
Laboratory for sending specimen	Identified laboratories as described in this chapter
Funding	• The expenses for activities related to AEFI surveillance, AEFI case management, transportation of vaccine and other AEFI related activities can be made from the available funds under PIP FMR code RCH 4-Immunization – S. No. 32 – SSRE (Surveillance Research Review Evaluation). • All expenses towards actual testing of vaccines in CDL Kasauli and Kolkata will be borne by the respective laboratories. • NIV Pune, NIV Mumbai and NIV Gorakhpur will bear the expenses related to actual testing of samples for adverse events occurring following JE, MR vaccination.
Reporting of laboratory results / reports	• The laboratory as a rule will forward a copy of the report to CDSCO, AC Immunization Division, MoHFW, State Immunization Officer, State Cold Chain Officer, and State drug authority. • Laboratories will also send a copy of the laboratory results to all persons with contact details. Complete address with pin code, phone and fax numbers and email address should be mentioned in the LRF (Laboratory request form).
Feedback of Laboratory results	DIO to share with drug inspector, medical officer reporting the case and the private health facility reporting the case
Decision to temporarily suspend the use of implicated batch of sample (only if there is suspicion of quality which is very rare)	The local drug authority representative together with the DIO and district AEFI committee in consultation with the SEPIO/State AEFI Committee, MoHFW, GoI

7.2.2 Packing of Samples

- Separate plastic zipper bags should be used for packing different vaccine and diluents.
- The name, age, date of collection, AEFI EPID number and point of collection of vaccines/ diluents should be mentioned on the label of each plastic zipper bag.
- All the packed zipper bags (separate for vaccines and diluents) should then be put in a bigger zipper bag.
- The big zipper bag should be placed in a card board box, tied with a string from all sides and an "official lac seal" affixed by the drug inspector, or if it is not available, the CMO (Figure 7.1).

Figure 7.1: Use of Official Seal

7.2.3 Documentation and Transportation of Sample to Laboratory

- The completed LRF (**Annexure 13**) also sealed with the same "official lac seal" should accompany the samples sent to the laboratory. The "official lac seal" ensures that the samples and details sent to laboratory are not tampered with or changed during transportation.
- Ensure that the completed investigation forms (CRF, CIF) also accompany the samples to the laboratory.
- Vaccines and diluents are tested simultaneously. Therefore, diluents of freeze-dried vaccines (BCG, MR, and JE vaccine) should be sent with the vaccine samples.
- The sample should be transported to the laboratory under cold chain (vaccine carrier with ice packs or thermocol boxes with icepacks), preferably through a messenger.
- CDL Kasauli accepts samples on all days of the week. The messenger carrying the samples to CDL Kasauli must insist on getting the `sample received receipt' for official record. This receipt will also provide details on the condition of samples received in the laboratory. (Issue of receipt will not be possible in cases when the samples are received on weekends).
- Samples may also be sent by courier service provider that has experience in handling biological products and can also guarantee delivery to CDL Kasauli within the stipulated time and condition.

Address for Shipment of Vaccines and Diluents

Director, Central Drugs Laboratory, Central Research Institute,
Kasauli - 173204, Himachal Pradesh.
Email: nclkasauli@gmail.com; Phone: 01792-272578/272046

Example of Vaccine/Diluent Collection

An AEFI occurred in district M following use of a 5-dose vial of MR vaccine at a session site. The District AEFI committee reviewed the case and decided to collect the implicated batch of MR vaccine and diluent for testing in CDL Kasauli. As per guidelines (Table 7.4), the team comprising DIO and Drug inspector planned to collect 60 vials of MR vaccine and 60 ampoules of MR diluent.

However, during the site visit, they were able to find only one partial and one unused vaccine vial of the same batch with the ANM. They, therefore, collected 59 unused MR vials from the PHC vaccine storage point. The total quantity required (i.e., 60 vials) was thus complete. The vaccine vials were then packed in different zipper bags and labelled mentioning the point from where they were collected. In this case, it was the session site and the PHC.

The next step was to collect 60 MR diluents. They could only collect 45 diluents of the implicated batch from the PHC and another 15 diluents were collected from the district vaccine store. The total quantity required (i.e., 60 diluents) was now complete.

Four equal sets of 15 vaccine vials and 15 diluents each were prepared and put into eight zipper bags and labelled.

One packet each of 15 vaccines and 15 diluents (properly zipped and labelled) were placed in a cardboard carton and sealed with the Drug Inspector's "official lac seal". This was sent under cold chain for testing to CDL Kasauli along with a LRF, CRF and CIF. The rest of the sets were packed and retained at different levels as per guidelines mentioned above.

Sending opened used/partially used vials to CDL Kasauli

Used (opened) vials are technically not required by the CDL Kasauli for testing. The sender is, however, encouraged to send the used vial (if available) to ensure that the same batch of the unused vials is being sent for testing. The opened vials are usually not tested because of the following reasons:

- Quantity of vaccine is often inadequate for testing
- Once the vials are opened, they become unsterile because of contamination from the surrounding environment
- Reconstituted vials cannot be tested beyond 4 hours
- Opened vials have weak legal sanctity.

As per existing Open Vial Policy of the MOHFW, all opened vials which have returned from a session should be segregated into two groups. One group of vials will have vaccines on which open vial policy is applicable and the second group will have vaccine vials on which open vial policy is not applicable. The vaccine vials on which the open vial policy is not applicable are to be stored in a plastic box clearly marked “not to be used” in the ILR. These vials should be discarded after 48 hours or before the next session whichever is earlier. In case of any reported AEFI, these vials should not be discarded and should be retained for investigation.

7.2.4 Dos and Don'ts for Collection of Vaccine/ Diluent Samples and Transportation

Dos

1. Collect unused samples only from the implicated (suspected) batch.
2. Send the implicated samples of vaccine and diluent to the laboratory affixed with "official lac seal".
3. Ensure that the accompanying LRF is also affixed with the "official lac seal".
4. Pack the diluents carefully and separately in a sealed packet.
5. Mention the point from where the vaccines/ diluents were collected on the label of each plastic zipper bag.
6. Ensure the name of the vaccine, batch number, manufacturing and expiry dates and other details on the label as affixed by the manufacturer are intact and clearly visible on all the vials/ ampoules of the samples.
7. The packing should be such that there is no breakage of vials. The small cartons in which the vaccines are supplied by the manufacturers may be used for this purpose. The vaccines should be packed in a plastic zipper bag and sealed. The zipper bag is then put in the vaccine carrier or thermocol box with ice packs. Dry ice may be used for OPV samples and NEVER for freeze sensitive vaccines.
8. The address of the CDL Kasauli should clearly be written on the box.
9. The samples should be accompanied with the LRF and CRF. CIF and other relevant records may be sent, if available.

Don'ts

1. Labels must NEVER be wrapped with adhesive tape or covered with any other labels on the vaccine/ diluent vials as shown in Figure 7.2.
2. There should be no wetting or mutilation of labels. Appropriate labels may be affixed on the zipper bags with vaccine samples inside.
3. The vaccines should not have expired at the time of receipt of vaccine in the laboratory.

Figure 7.2: Examples of Vials/Diluent Not to be Used

7.3 Testing of Syringes, Needles & Vitamin A at CDL, Kolkata

CDL Kolkata is the identified laboratory where implicated samples of AD syringes/ reconstitution syringes and vitamin A, are tested for standard sterility and physical parameters. The testing of the AD syringes/ reconstitution syringes and vitamin A should be initiated following decision by the district or state AEFI committee and/or when there is clear basis of suspicion and NOT as a routine procedure. Laboratory tests are performed and results dispatched to the sender approximately within 60 days of receipt of the samples.

7.3.1 Sample Collection

A representative of the local drug authority (drug inspector) should be involved in the collection of samples as per Drugs and Cosmetics Rules and transfer of sealed samples to the CDL Kolkata. The sample of implicated AD syringes, reconstitution syringes or vitamin A that are sent should be of the same manufacture and batch number. The samples should be collected in four equal sets - one set to be sent for testing; one set retained at the point of collection and two sets retained with the drug inspector (Table 7.6). The samples can be sent through reliable courier or postal services. Cold chain is NOT required.

Table 7.6: Quantity of Unused Syringes, Needles & Vitamin A for testing

Sample	Unused Quantity of Implicated Batch
AD Syringes	Four sets of 50 pieces each (total 200) • 50 pieces to be sent to CDL Kolkata • 50 pieces to be retained at the source of collection • Two sets of 50 pieces each (total 100) to be retained by drug inspector (local drug authority)
Reconstitution Syringes	Four sets of 50 pieces each (total 200) • 50 pieces to be sent to CDL Kolkata • 50 pieces to be retained at the source of collection • Two sets of 50 pieces each (total 100) to be retained by drug inspector (local drug authority)
Vitamin A	Four sets of two 100 ml bottles (total eight bottles) • Two bottles for CDL Kolkata • Two bottles to be retained at the source of collection • Four bottles to be retained by drug inspector (local drug authority)

7.3.2 Packing, Documentation and Shipment

The used samples (AD syringes/ reconstitution/ disposable/ Vitamin A) if available should be sent along with the unused batch of the same manufacturer. Both items should be sealed in separate packets, labelled with the site of collection, placed in a card board box, securely tied with a string with an "official lac seal" affixed by the drug inspector. The CMO's "official lac seal" may be used if the "official" lac seal of the drug inspector is unavailable.

Address for shipment of syringes, needles and vitamin A:
The Director,
Central Drug Laboratory, Ministry of Health and Family Welfare, Govt. of India
3, Kyd Street, Kolkata – 700016.
Email: cdlkol@cdsco.nic.in Phone: 033-22299541, Fax: 033-222 99380

The samples should be sent with completed LRF form and CRF. CIF and other relevant records may be sent if requested.

In case of Vitamin A samples, the used bottle, if available, can also be sent along with the unused, sealed bottles of Vitamin A properly packed to avoid breakage or spillage during transportation.

Important Considerations

- Health authorities need to coordinate with the police / other investigating departments and acquaint them with the National AEFI guidelines.
- All original documents must be retained by the medical officer in charge. Documents requested by the police / other investigating agencies should be shared as attested copies.

Summary

- Biological samples from the patient and vaccines, diluents and logistics (syringes and Vitamin A) can be sent for testing during an AEFI investigation.
- The decision regarding the testing of biological specimens is taken by the treating physician, depending on the clinical signs and symptoms and differential diagnosis.
- Laboratory testing for implicated vaccines / diluents / logistics should not be routinely requested. It should be requested only on a clear suspicion regarding their quality e.g. cluster of AEFI cases, increase in vaccine reactions, public/community concern.
- The DIO and drug inspector should be involved in the collection of adequate quantity of implicated vaccine/ diluent samples.

8 Causality Assessment of AEFIs

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine(s) received or the vaccination process. This does not necessarily prove or establish whether or not a definite relationship exists, but only ascertains a degree of association with the vaccine/vaccination. It is nevertheless a critical part of AEFI monitoring and enhances confidence in the national immunization programme. Programme managers and vaccinators would like to know if the AEFIs are due to the vaccine or the vaccination process, or coincidental. Vaccine recipients want to know whether what they have experienced was due to the vaccine or something else. They may believe that because the event followed vaccination, it may be causally linked to vaccination. It can be difficult to explain that this might not have been the case. Causality assessment provides a more objective explanation that may reassure the vaccinee (and/or family members) and facilitate better management of the event. It also helps to define the safety profile of the concerned vaccine. In essence, whether an AEFI might be attributable or not to the vaccine/vaccination determines what steps need to be taken to address the event.

Causality assessment is important for:

- identification of vaccine-related reactions
- identification of immunization error-related problems
- identification/exclusion of coincidental events
- detection of signals for follow-up, testing of hypothesis and research
- validation of pre-licensure safety data of vaccines by comparison with data obtained from AEFI surveillance related to vaccine-associated AEFIs

The quality of the causality assessment depends on three factors:

1. the performance of the AEFI surveillance system in terms of responsiveness and effectiveness, especially the quality of case reporting and investigation
2. the availability of adequate medical information including clinical investigations and follow-up of cases, and access to background information on population disease/illness rates in the absence of vaccination
3. the quality of the causality review process, including access to appropriate expertise.

With inadequate or incomplete case information, a causality assessment can:

- either not be performed (ineligible) or
- the case can be deemed unclassifiable due to lack of crucial information

Even with availability of reasonably complete information, the relation of a vaccine to the reported event may at times be indeterminate due to:

- lack of clear evidence of a causal link or
- conflicting external evidence or
- other inconsistencies.

Nevertheless, these determinations should be recorded because reporting of more cases may lead to a stronger signal and a plausible hypothesis, or stronger refutation (contradiction) of any link.

In summary, causality assessment usually will not prove or disprove an association between an event and immunization. It is meant to assist in determining the level of certainty of such an association. This is an evolving science and the classification following causality assessment is based on the existing available scientific knowledge and evidence. A definite causal association or absence of association often cannot be established for an individual event. With all its limitations, it is a crucial component of the AEFI surveillance system of a country and helps maintain confidence in vaccine safety while detecting vaccine-related events, programmatic errors and possible signals.

8.1 Who Should Conduct the Causality Assessment?

The causality assessment process should be performed by a team whose areas of expertise include at the least, paediatrics, epidemiology, medical pharmacology, forensic medicine, and pathology. Other desirable expertise includes microbiology, neurology and immunology. Persons familiar with the immunization programme and cold chain should also be included. All members of the team should have been trained in the process of causality assessment. In addition, experts from other specialities, such as medicine, neurology, cardiology, obstetrics and gynaecology may be co-opted for the causality of specific events. The committee needs to be independent and work in close collaboration with the immunization program (state and/or national level) and National Regulatory Authority (NRA). The SEPIO should not be involved in the causality assessment procedure except to ensure that cases put up for causality assessment to the members are complete with all necessary records available for conducting the causality.

8.2 Establishing AEFI & Vaccine Causal Relationship: The Criteria

Criteria for causality are generally considered to have been derived from work by Bradford Hill in 1965 as minimum conditions necessary to provide adequate evidence in support of a causal relationship. While he indicated nine criteria, the following eight are most relevant to the question "can the given vaccine cause a particular event", with the first being essential.

Temporal Relationship

The vaccine exposure must precede the event occurrence. Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must

always precede the occurrence of the disease. This is the only absolutely essential criterion in causality. An exception to this rule is onset of signs/symptoms related to immunization triggered stress response that may sometimes happen before vaccination.

Biological Plausibility

Biological plausibility may provide support for or against a causal relationship. The association should be compatible with existing theory and knowledge related to how the vaccine works, e.g. the live attenuated measles containing vaccines can cause mild fever and rash, very similar to the actual measles infection.

Strength of Association

The association should have met statistical significance in scientific studies to suggest that association between the vaccine and an event is not simply a chance occurrence. The stronger the association, more likely the relation is causally associated.

Consistency of Association

The association is consistent when results are replicated in studies in different settings, among different population using different methods.

Specificity

The vaccine is the only cause of the event that can be found in that particular case. An example is excessive swelling in the same limb in which DPT vaccine was administered.

Definitive Proof that the Vaccine Caused the Event

Clinical or laboratory proof that the vaccine caused the event. It is most often found in case of live attenuated vaccines. An example would be isolation of rubella vaccine strain in CSF in a case of encephalitis following measles-rubella vaccination.

Consideration of Alternate Explanations

In doing causality assessment, all reasonable alternative etiologic explanations need to be considered.

Prior evidence that the vaccine in question could cause a similar event: Review of data related to pre-licensure studies and other published literature could reveal prior evidence that a particular clinical event is associated with the vaccine given. A review of AEFI surveillance database maintained nationally or globally can also provide evidence for this.

Occasionally, there may be instances when a particular event was revoked in a beneficiary when vaccinated with the same vaccine inadvertently. An example is Guillain-Barré Syndrome occurring in the same individual within weeks of inadvertent administration of tetanus vaccine on three separate occasions. It is important to ensure that vaccinations are not to be repeated to test the recurrence of the same event with the same vaccine. Rather, proper history should be taken to ensure that any contraindications are considered before vaccination.

8.3 Causality Assessment Method

All reported severe and serious AEFI cases for whom the investigation is completed should undergo causality assessment[35]. Before sending a case for causality assessment, each case needs to be screened to check if it fulfils the basic requirements of eligibility for causality assessment. Please refer to section 8.8.1 for details.

There are four steps in causality assessment. The steps and their purpose are outlined below:

- **Step 1**: Eligibility: to determine if the AEFI case satisfies the minimum criteria to be eligible for causality assessment.
- **Step 2**: Checklist: to systematically review the relevant and available information to address possible causal aspects of the AEFI.
- **Step 3**: Algorithm: to obtain a trend as to the possible causality with the information gathered in the checklist.
- **Step 4**: Classification: to categorize the AEFI's association to the vaccine or vaccination based on the trend determined in the algorithm.

Step 1: Eligibility

Going through Step 1 will ensure that the case fulfils the following criteria to make it "eligible" for causality assessment:

1. The AEFI case investigation should have been completed. Premature causality assessment with inadequate information can cause errors in classification of the event.
2. All vaccines that were administered before the event should be identified.
3. All details of the case should be available at the time of assessment. These include documents pertaining to the clinical records, laboratory investigations as well as complete autopsy findings/verbal autopsy as appropriate. Statements from treating physician, vaccinator, community members and parents will help to get information which can assist causality assessment.
4. There must be a "valid diagnosis" (see below) for the adverse event. This should preferably be the disease condition caused, but could also be a clinical symptom or sign, or an abnormal laboratory finding.

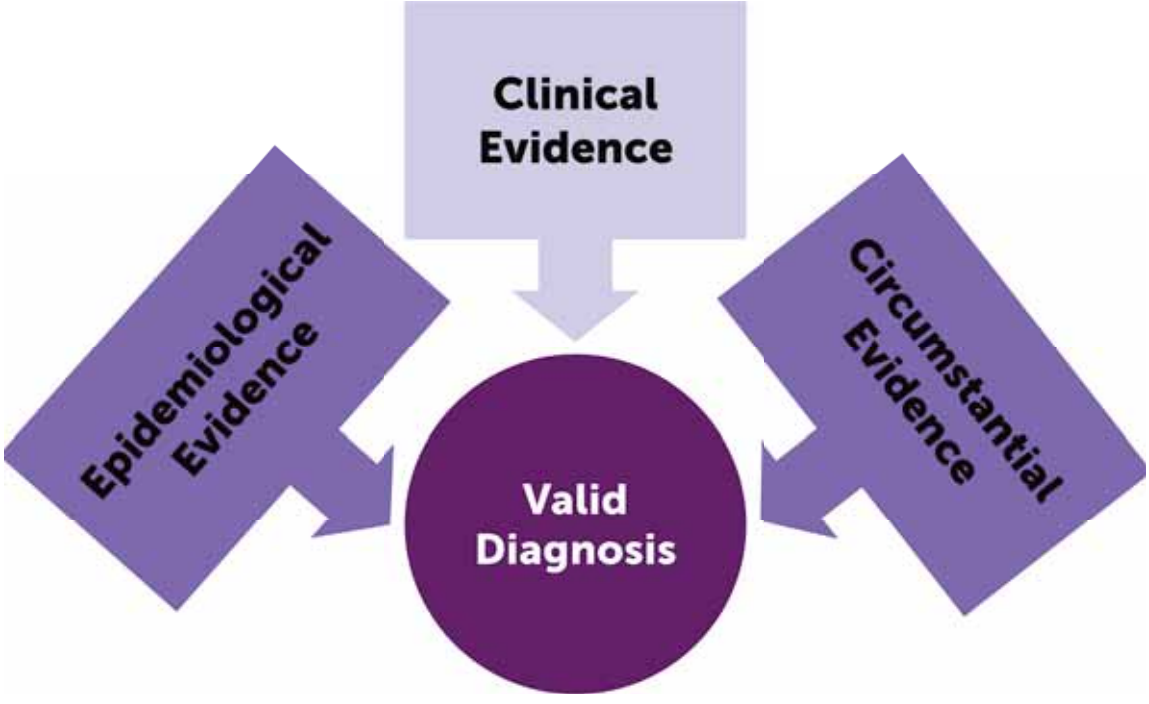
The assessor should first confirm that the vaccine was administered before the event occurred by comparing the time of vaccination and the time of onset of signs and/or symptoms related to the event being assessed. He/she should then carefully go through all records of the case and create a case summary, recording the date and time of vaccination, the vaccine(s) administered, onset of first symptom as well as chronology of events.

Before attempting causality assessment, it is essential to be clear on the "valid diagnosis" of the reported AEFI. The valid diagnosis could be a disease, clinical sign, symptom or abnormal laboratory finding. If multiple symptoms, signs or laboratory abnormalities are available, as far as possible, a suitable single valid diagnosis is made out of the available information instead of moving ahead with one feature as the diagnosis. For example, if a recipient develops

[35] *Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification (Second edition). Geneva: World Health Organization; 2018*

pain, swelling and redness at vaccination site, it would be appropriate to write 'injection site cellulitis' as the valid diagnosis. The diagnosis should preferably meet a standard case definition for the disease process being assessed. If available, it is best to adopt one of the Brighton Collaboration case definitions[35] . However, if this is not possible, case definitions can be adapted from the standard medical literature, national guidelines or local clinical practice. While arriving at a valid diagnosis, consider not only the clinical information available for the case, but also the epidemiological and circumstantial evidence (Figure 8.1) which will be recorded in case investigation forms and investigation reports. If the reported event does not have a valid diagnosis, it may not be possible to adequately categorize the AEFI and additional information should be collected to arrive at a valid diagnosis.

Figure 8.1: Evidences for Arriving at a Valid Diagnosis



The Brighton Collaboration is an international voluntary collaboration of scientific experts, launched in 2000. It facilitates the development, evaluation and dissemination of high-quality information about the safety of human vaccines. The main objectives of the collaboration are:

1. To raise global awareness of the availability of standardized case definitions and guidelines for data collection, analysis and presentation, and to educate about the benefit of and monitor their global use and to facilitate access,
2. To develop single standardized case definitions for specific AEFIs,
3. To prepare guidelines for data collection, analysis and presentation for global use,
4. To develop and implement study protocols for evaluation of case definitions and guidelines in clinical trials and surveillance systems.

36. www.brightoncollaboration.us

The process described here envisages the causality assessment of an individual AEFI case with a particular vaccine. In case of multiple co-administered vaccines, use the information about known side effects of administered vaccines, their window period, as well as biological plausibility to identify which vaccine would most likely be related to the event being assessed. Causality is then assessed for the most plausible vaccine leading to the event. If it is not possible to identify a single vaccine that could have led to the event, causality assessment may have to be done for each vaccine separately.

If more than one valid diagnosis is made for the same case, which might have been caused by same or different vaccines, causality assessment should be done for each valid diagnosis and corresponding suspected vaccine, separately. For example, if a case of seizure on day one and fever with rash on day 6-7 is reported following DPT-booster and MR-2nd dose, then causality assessment has to be done separately for seizure and for fever with rash with DPT and MR vaccines respectively.

At the successful completion of this stage, the reviewers should define the "causality question" (Figure 9). It is recommended to write the name of single vaccine in this question. Write the 'valid diagnosis' in the space after the name of the vaccine.

Some examples of causality assessment questions are as follows:

Has the _____ vaccine / vaccination caused _____?
Co-administered vaccine (if any):

Examples of Causality Questions

- "Has the vaccine A caused meningitis?" (An example of a disease).
- "Has the vaccine B caused thrombocytopenia?" (An example of a laboratory finding)
- "Has the vaccine C caused hepatomegaly?" (An example of an unfavorable or unintended sign)
- "Has the patient complained that the vaccine D caused itching?" (An example of a symptom)

Important: 'Death' is not a valid diagnosis. The pre-existing illness or the circumstances leading to death should be mentioned as a valid diagnosis.

If more than one vaccine has been administered, the name of the vaccine likely to have caused the event should be written in the main question, while the other vaccine (s) can be written against the co-administered vaccines. An example is given below:

Has the pentavalent vaccine / vaccination caused febrile seizure?
Co-administered vaccine(s) (if any): OPV

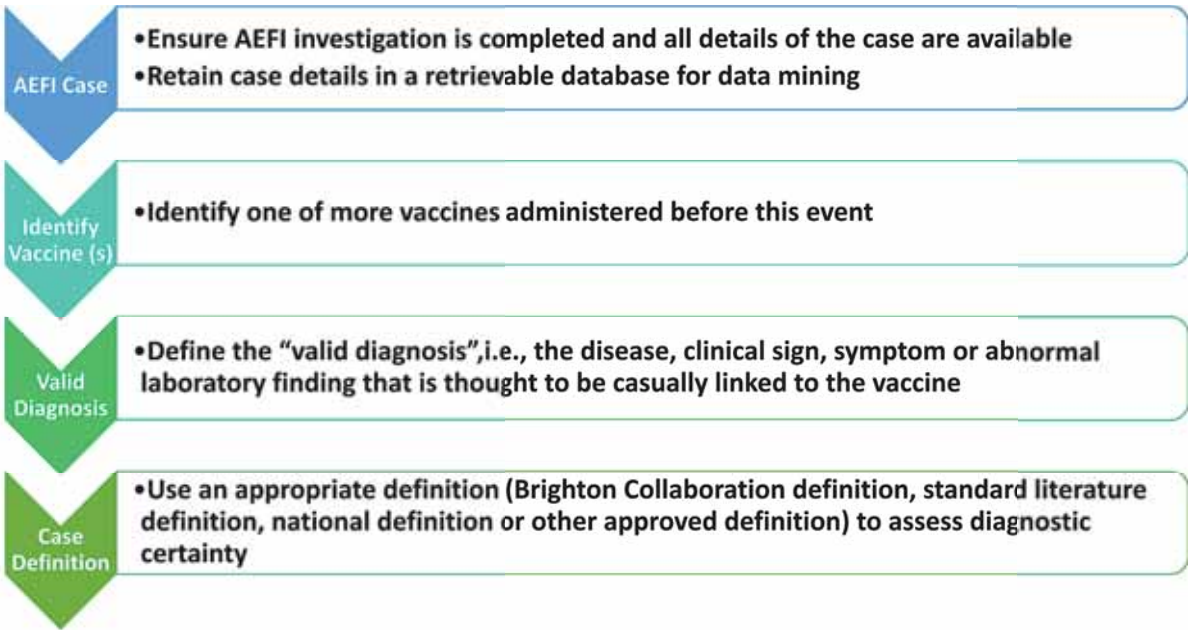
As discussed earlier, when faced with multiple presumptive diagnoses, the reviewer should do a separate causality assessment for each diagnosis. An example is when a case is reported with an abscess as well as a febrile seizure following hepatitis B vaccination.

1. Has the hepatitis B vaccine / vaccination caused an abscess?
Co-administered vaccine(s) (if any):

2. Has the hepatitis B vaccine / vaccination caused febrile seizure?
Co-administered vaccine(s) (if any):

At this point of the assessment, the assessor has to make a decision whether the information that is available at hand is sufficient to proceed (eligibility for assessment), (Figure 8.2).

Figure 8.2: Causality Assessment: Eligibility



If not, the assessment should be temporarily kept in abeyance until the basic information is obtained. It is important that, if an AEFI appears to not meet the eligibility criteria because of inadequate information, attempt should be made to collect any additional information required from the districts in order to ensure that the case can be properly assessed for eligibility. Causality should not be attempted when the CRF and/or the CIF are not available.

Cases deemed "ineligible" for causality assessment are those where the amount of information initially available to the assessor is so limited that the causality question cannot be framed & causality cannot be initiated. Cases can be deemed "ineligible", if:

1. CRF and/or CIF are not available.
2. The names of vaccines administered are not available or not clear.
3. Information available in the case reports/records is so scanty that it does not allow identification of a valid diagnosis.

Step 2: Checklist

This checklist (refer Table 8.1) is filled *keeping the causality assessment question developed at the end of Step 1 in mind*. The checklist is designed to assemble information on patient-immunization-AEFI relationships in the following key areas:

- Is there evidence for other causes?
- Is there known association of the event with the vaccine/vaccination in the medical literature, and if so, did the event occur within a plausible time window?

- Is there strong evidence against a causal association?
- Other qualifying factors for classification such as previous history of a similar event, the background rate of the event, pre-existing, present and past health conditions, potential risk factors, other medications, exposure to triggering factors, etc.

It is essential that all questions in the checklist should be answered with any one of the options – "Yes", "No", "Unknown'' or "Not applicable". If the response of any question is "Yes", it is essential to provide an explanation in the "remarks" column. Provide explanations for responses other than "Yes" if it is important to justify / determine causality.

The checklist is filled keeping in mind the specific causality question which has been framed. Information used to fill up the checklist can be culled out from the available case documents and various reference materials such as WHO vaccine information sheets, WHO vaccine reaction rates information sheets[37], Brighton Collaboration definitions[38], etc.

I. Is there strong evidence for other causes?

In judging whether a reported association is causal, it is necessary to determine the extent to which researchers/causality assessment committee have taken other possible explanations into account and have effectively ruled out such alternative explanations.

I.a In this patient, does the medical history, clinical examination and /or investigations, confirm another cause for the event?

A review of medical records including laboratory tests and AEFI investigation forms help to identify other conditions that could have caused the event. For example, a case of seizure occurring within 24 hours of receiving pentavalent vaccine may be thought to be vaccine product related. However, if blood test reports show low calcium levels and treatment records show no seizures following treatment aimed at normalizing calcium levels, another cause for the event can be hypocalcaemia.

II. Is there a known causal association with the vaccine or vaccination?

The questions in this section will help the assessor to determine if the event is known to be related to the vaccine in any way: product related, quality defect related, immunization error related, or stress related. If no such association is known, the event is likely to be coincidental. It is important to be alert to detect new events with unknown causal association (signals) particularly with new vaccines that have been recently developed/ approved for use.

Vaccine Product(s)

II.a ***Is there evidence in published peer reviewed literature that this vaccine may cause such an event even if administered correctly?***

Refer to the vaccine information sheet of WHO and the package insert of the vaccines to find a list of common vaccine reactions that are known to be associated with that vaccine

37. https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/guidance/reaction-rates-information-sheets
38. https://www.brightoncollaboration.org/case-definitions

and their expected frequency. These documents are available in the AEFI reference tool kit and also at https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/guidance/reaction-rates-information-sheets. Some reaction rates which are not available in the information sheets may be available in published literature. For newer vaccines, a search of recently published medical literature may yield important information.

It is rare for vaccines to cause serious adverse events due to the vaccine's inherent properties when administered correctly. For example: A causal association between the measles-mumps-rubella (MMR) vaccine and idiopathic thrombocytopenic purpura (ITP) was confirmed using immunization/hospital admission record linkage. The absolute risk within window period (2-6 weeks) of immunization was 1 in 22,300 doses.

II.b ***Is there a biological plausibility that this vaccine could cause such an event?***

Biological plausibility or biological mechanisms as an additional qualifying factor can be invoked only when a symptom/sign/ laboratory finding are similar and consistent with the natural history and pathophysiology of the infection or antigen. Evidence regarding biological plausibility, however, can never prove causality. At best, biological plausibility adds an additional piece of supportive evidence.

For example:Acute cerebellar ataxia is a proven complication of wild type varicella zoster virus (VZV) infection with an estimated incidence of five per 1,00,000 infections among children aged five years and under. Since the wild virus causes acute cerebellar ataxia, it is biologically plausible that the attenuated vaccine virus could also result in this complication of VZV infection in certain vaccinees. However, existing evidence is still not sufficient to confirm or reject this hypothesis so it remains a theoretical possibility based on biological plausibility.

II.c In this patient, did a specific test demonstrate the causal role of the vaccine?

This condition is also fulfilled occasionally. An example would be isolation of *Mycobacterium bovis* vaccine strain in children who develop suppurative adenitis following BCG vaccination at non-recommended sites or with improper technique.

Vaccine Quality

II.d Could the vaccine given to this patient have a quality defect or is substandard or falsified?

A vaccine quality defect-related reaction is an AEFI that is caused or precipitated by one or more quality defects of the vaccine products or its administration device as provided by the manufacturer.

Death due to a vaccine quality defect has been only infrequently found through the course of history, primarily due to incomplete inactivation of a live vaccine. Almost all such cases have occurred over 60 years ago. For example, in 1929 in the city of Lubeck, Germany, 72 of 252 infants vaccinated with BCG died because of contamination of the vaccine with a live human tuberculosis strain.

In April 2010, Australia and New Zealand reported increase in number of febrile seizures in children below 5 years of age following vaccination with Fluvax (manufactured by CSL, Australia), a trivalent influenza vaccine as compared to two other flu vaccines used in Australia at that time. Fluvax was withdrawn from the market. Subsequent studies revealed that a standard method of manufacture preserving strain-specific viral components of the new influenza strains may have contributed to heighten the immune activation of innate immune cells associated with febrile seizures in a small proportion of children[39].

Sometimes vaccines are falsified and are designed specifically to deceive patients, healthcare professionals and procurers into thinking that they are genuine. Others are substandard due to poor manufacturing practices or degradation of the product during distribution and storage. It is important that all steps are taken to ensure that all administered vaccines are authentic and procured from trusted and licensed outlets. Prior to vaccination, the responsible immunization staff should:

- examine the packaging for its condition, spelling mistakes or grammatical errors etc.
- check registration number, manufacturing and expiry dates as shown on the label
- ensure the product looks correct, and is not discoloured, degraded etc.

Substandard (authorized vaccines that fail to meet either their quality standards or specifications) or falsified vaccines (vaccines that deliberately/fraudulently misrepresent their identity, composition or source) have been detected from all over the world. WHO has received reports of falsified vaccines for yellow fever, meningitis and rabies. An example is the reporting of falsified AMARIL yellow fever vaccine in south-east Asia in 2016[40]. The yellow fever vaccine is manufactured by Pasteur Institute, Dakar, Senegal. There were a number of falsified elements on the packaging, including a falsified expiry date, as well as other inconsistencies that were identified through visual inspection of photographs of the falsified products, as compared to the genuine products.

Immunization Error

Immunization error describes an AEFI that is caused by inappropriate vaccine handling, prescribing or administration and that therefore, by its nature, is preventable. In many countries, several serious AEFI are precipitated by immunization errors. During any AEFI investigation, the first priority is to rule out an immunization error. An immunization error-related reaction may lead to a solitary event or a cluster of events associated with immunization.

II.e In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient, etc.)?

It is essential that vaccines are used in accordance with the indications, contraindications, dosage, storage conditions, reconstitution procedures etc. outlined in the package insert. Each vaccine from a different manufacturer may have different specifications and failure to comply with them can result in AEFI.

39. *Role of viral RNA and lipid in the adverse events associated with the 2010 Southern Hemisphere trivalent influenza vaccine; S. Rockman et al. / Vaccine 32 (2014) 3869–3876*
40. https://iris.who.int/bitstream/handle/10665/331042/DI301-46-55-eng.pdf

For example:

- systemic and/or local reactions following administration of an incorrect dose;
- systemic and/or local reactions following administration of the wrong product or administration to an individual in an incorrect age group;
- vaccine failure, or systemic and/or local reactions following administration of the product that was stored in non-recommended storage conditions;
- vaccine failure if a live attenuated product is given too soon after blood products or at an age when maternally transferred antibody could interfere with the replication required to induce an immune response
- failure to screen and identify absolute contraindication which may have caused an expected AEFI

II.f In this patient, was the vaccine (or diluent) administered in an unsterile manner?

Poor vaccination technique e.g. touching the hypodermic needle while injecting can cause abscess. Administration of the contaminated vaccine may lead to either local (cellulitis or abscess) or systemic (sepsis or toxic shock syndrome) adverse reaction. Abscess is the most common programme error which is reported. Solitary abscesses occurring sporadically and not related to a particular vaccinator, session site, batch number are not alarming. However, if analysis of the AEFI registers at PHC/block level shows that abscesses are being reported from a particular subcenter or is related to a particular vaccinator, then this needs to be investigated by observing the injection practices of the sub-center/ vaccinator. It is important to be vigilant, regularly check AEFI registers for patterns/trends to pick up increasing occurrence of abscesses. The bacterial culture of the vial (if available) or local tissue or pus may confirm the source of the infection.

II.g In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?

Abnormal colour, turbidity or presence of visible contaminants may be the first indication that the vaccine contents are abnormal or unsterile and may have caused an AEFI such as injection site abscess. It is important to talk to the vaccinator and ask whether any abnormality in the vaccine vial or diluent contents was noticed and also examine the remaining contents of the same vial and other vials of the same batch in the PHC cold chain room.

II.h When this patient was vaccinated, was there an error in vaccine constitution/ preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling, etc.)?

AEFIs including deaths have resulted because of accidental use of the wrong product or the wrong diluent. This may occur because of improper storage and/or improper selection. Vaccine failure can result if the entire content is not dissolved when freeze-dried vaccines are used or if the cold chain is not maintained properly. Errors in drawing up vaccine into syringes may result in AEFI due to excess filling or vaccine failure due to inadequate filling.

There have been instances where contents of a vial containing another drug (such as insulin, antihypertensive, muscle relaxant, etc.) in an ampoule was mistakenly used as the diluent for reconstitution of freeze-dried vaccines. As a result, recipients suffered adverse events, mostly in clusters which have been damaging to the immunization programme.

II.i In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?

Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent where applicable) may result in:

- vaccine failure as a result of inactivation of the active vaccine components;
- systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines.

Reconstituted vaccines used beyond the prescribed time and recommended maintenance conditions can result in vaccine failure and/or disease in the recipient (e.g. toxic shock syndrome). Infrequently, children immunized with a contaminated vaccine (usually with the bacterium Staphylococcus aureus) become unwell within a few hours. Injection site inflammation (redness, swelling and pain), high fever, rigors, vomiting, diarrhoea, rash and septic shock (toxic shock syndrome) may occur. Deaths have been reported due to septic shock. Bacterial culture of the vial contents, if still available, or of local tissue can confirm the source of the infection.

Usually, this happens when:

1. reconstituted vaccines are used beyond the recommended time (>4 hours)
2. reconstituted vaccines are not kept under proper cold chain at the session site
3. reconstituted vaccines are used in more than one session sites
4. syringe used for reconstituting a vaccine vial is reused for reconstituting other vaccine vials

For cases with suspected toxic shock syndrome, it is critical to have information about the sequence and timing of administration of vaccine doses from a vial along with the vaccine reconstitution timing, vaccine storage during the immunization session and the ambient temperature. It is also important to assess if syringes are being reused for reconstitution (due to non-availability or shortage at the session site) as this can also inadvertently lead to toxic shock syndrome due to contamination of vaccine at the time of reconstitution.

II.j In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size, etc.)?

A variety of AEFI may result from incorrect administration of a vaccine. For example:

- neurological, muscular, vascular or bone injury from the use of an incorrect injection site, equipment or technique;
- systemic and/or local reactions following administration of an incorrect dose;

- sterile abscess following subcutaneous instead of intramuscular injection of alum adjuvanted vaccines – usually a result of using a needle that is too short to reach the muscle layer.
- administration of injectable vaccines orally or oral vaccines as injections.

Immunization Anxiety (Immunization Triggered Stress Response - ITSR)[41]

There may be some AEFIs which may not manifest with typical symptoms of anxiety. The term "immunization anxiety related reaction" used earlier does not capture all the elements of events arising from anxiety about the immunization. Therefore, such reactions are now termed "Immunization Triggered Stress Response (ITSR)". The word immunization is used in this context to describe the process of administering the vaccine and to include the time period before, during and after vaccine administration.

1. An acute stress response is an internal physiological response to a threat which manifests with variable severity of symptoms that may range from mild feelings of worry and "butterflies" in the stomach to sympathetic stimulation: increased heart rate, palpitations, difficulty in breathing or rapid breathing (hyperventilation). An individual's stress response is affected by a number of factors including their understanding and interpretation of the situation, their emotional response, their memory of previous experiences, genetics, gender and environment.
   a. Hyperventilation syndrome (rapid breathing) may be part of an acute stress response. The presenting features are dyspnoea (shortness of breath), chest pain, paraesthesia (tingling sensation) in the fingers, light-headedness, dizziness and headache.
   b. Syncope and non-epileptic seizures characterized by pseudo-absence spells may occur. Adolescent girls are usually affected, and episodes are associated with anxiety or as a component of an anxiety disorder. Episodes often recur, and the diagnosis may be missed and ascribed to cardiac or another life-threatening disorder.
   c. A vasovagal reaction manifests as symptoms of mild dizziness or a brief loss of consciousness (syncope) because of insufficient blood flow to the brain after decrease in blood pressure due to a decreased heart rate or vasodilatation of blood vessels. It may be associated with prodromal symptoms such as nausea, sweating or pallor. A vasovagal reaction results in bradycardia and/or peripheral vasodilation with hypotension, which reduces the blood flow to the brain. The symptoms experienced include dizziness, blurred vision and syncope. Loss of consciousness usually lasts for less than 20 seconds but may last up to several minutes. This is a benign reaction with rapid recovery.

2. Conversion disorders (now called dissociative neurological symptom reaction– DSNR) is characterized by disruptions in sensation and control of bodily movements with no identifiable organic cause. The symptoms and signs can include weakness or paralysis, abnormal movements or limb posturing, gait irregularities, speech difficulties and non-epileptic seizures with no apparent physiological basis. These features may take hours to days to develop after immunization. DSNR appear to be more common in females.

41. *Immunization stress-related response: A manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization. Geneva: World Health Organization; 2019*

They are not typically diagnosed in infants; in children, DNSRs typically manifest with a single symptom. They are a result of interactions of numerous factors at various levels: psychological factors (e.g. history of abuse, traumatic experiences); vulnerability (e.g. age, personality, gender, pre-existing anxiety or depression); factors that shape manifestation of symptoms (e.g. witnessing symptoms in others); triggering factors (e.g. situations, circumstances) and factors that explain why the symptoms persist (e.g. coping strategies).

Immunization anxiety reactions can occur singly or in clusters. Adolescents, especially if immunized in mass clinical settings, are more prone to have anxiety-related vasovagal reactions resulting in fainting, sometimes accompanied by tonic-clonic seizure-like movements (pseudo-seizure).

An Anxiety Cluster

A session was being conducted in a school some distance away from a Primary Health Centre (PHC) in a district in India, during a Japanese Encephalitis mass vaccination campaign targeting children in the age group 1 - 15 years.

Eight children who received the vaccine complained of giddiness, tingling sensation and numbness of the upper and lower limbs and weakness 30 minutes after vaccination. It started with one child complaining of giddiness and weakness, followed soon by similar complaints from seven other children sitting in the same class as this child. Some among these also reported tingling sensation and numbness of upper and lower limbs. On examination, no organic cause of the events was found. Children were reassured and provided Oral Rehydration Solution and a meal at the PHC. All eight children were discharged after four hours. Twenty-four other children vaccinated in the same session did not have any complaints.

After investigations, it was concluded that this was due to immunization anxiety. There were no reports of similar events with the batch of vaccine related to this incident.

II.k In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)?

The types of reactions caused by immunization stress responses include, but are not limited to, acute stress responses, vasovagal reactions and conversion disorders.

II (time). If "yes" to any question in II, was the event within the time window of increased risk?

II.l In this patient, did the event occur within a plausible time window after vaccine administration?

It is important to confirm if the event took place within a "plausible" time window of increased risk. This is applicable to all questions under II. For example:

- The "plausible" time window for VAPP is between 4 and 30 days. A case classified as a recipient VAPP is a person who has:
  i) onset of acute flaccid paralysis (AFP) 4-30 days after receiving OPV,

ii) Sabin virus isolated and
iii) with neurological sequelae compatible with polio 60 days after the onset of paralysis.

Thus, cases with AFP onset less than 4 days or over 30 days after receiving OPV and isolating Sabin virus in the stool are not classified as recipient VAPP.

- A case of febrile seizure within 5 days following Measles – Rubella vaccination will not be assessed as vaccine-product related as the "plausible" time window of fever and seizures following MR vaccination is 5 to 12 days.

III. Is there strong evidence against a causal association?

III.a Is there a body of published evidence (systematic reviews, Global Advisory Committee on Vaccine Safety-GACVS reviews[42], Cochrane reviews etc.) against a causal association between the vaccine and the event?

An AEFI that is initially thought to be due to a vaccine may, after investigation, be found to be explained by a similar manifestation caused by another factor. For example:

- A 2003 Institute of Medicine (IOM) report "Immunization Safety Review: Vaccination and Sudden Unexpected Death in Infancy." The committee reviewed scientific evidence focusing on sudden unexpected death in infancy and looked for possible relationships between Sudden Infant Death Syndrome (SIDS) and vaccines. Based on all the research findings they reviewed, the committee concluded that vaccines did not cause SIDS or increase the risk of SIDS.
- In recent years, some researchers hypothesized that measles vaccine may be associated with autism. A series of studies were reviewed by the GACVS and also the IOM Committee to review adverse effects of vaccines. Both groups concluded that no evidence exists of a causal association between MMR vaccine and autism or autistic disorders.

IV. Other Qualifying Factors for Classification

Sections I to III outline the strong evidence for or against causality for most cases of AEFI. Below are some additional factors that support the above observations. If the AEFI is still unclassified, these qualifying factors provide reviewers with indications on causality.

IV.a In this patient, did such an event occur in the past after administration of a similar vaccine?

The occurrence of an AEFI after a previous dose of a similar vaccine should be handled cautiously. There have been cases of urticaria reported in children following vaccination with MR vaccine at age 16 to 24 months. When history of adverse reactions following previous vaccinations was properly elicited, parents reported similar skin manifestations following MR vaccination at 9 months of age.

Rotavirus vaccination is contraindicated in an infant with a history of intussusception, irrespective of whether the infant had been given rotavirus vaccine dose in the past. In documented cases of anaphylaxis and encephalopathy, children should not be revaccinated with the same vaccine or same antigen-containing vaccine.

42. https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/committee-reports

IV.b In this patient did such an event occur in the past independent of vaccination?

It is important to verify if a similar event occurred in the vaccinee and family in the past independent of immunization. For example, if a 24-month-old child receives MMR immunization and two days later presents with a diagnosis of atopic dermatitis, a careful clinical history may reveal that the child may have developed atopic dermatitis previously and had experienced frequent flares in the past.

IV.c Could the current event have occurred in this patient without vaccination (background rate)?

Knowledge of the background incidence of events which may occur in temporal relationship with a vaccine is essential for assessing a cluster of events in terms of the strength of the signal it may provide.

For example:

- In Israel, during the early phases of the annual influenza immunization campaign in October 2006, four deaths occurred among elderly vaccinees and the campaign was temporarily halted for an investigation. It was determined that the expected death rate among similarly aged vaccinees within seven days of a vaccine exposure was 0.01 to 0.02%. During several years prior to this apparent signal, the expected death rate had been similar (0.01 to 0.02%). The background rate for death in the population was relatively high as a result of age (>75 years) and comorbid conditions (e.g. diabetes, cardiovascular disease, homebound status). It was thus concluded that influenza vaccine did not confer any additional risk of mortality in this population.

- In the United States, each year approximately 1,400 infants under 12 months of age are hospitalized for intussusception. The expected number of cases, or background rate, of intussusception is 18 to 43 per 100,000 per year for unvaccinated children aged 6–35 weeks. The first rotavirus vaccine (RotaShield - rotavirus, live, oral, tetravalent – Wyeth) was licensed and recommended for routine use in the US by the Advisory Committee on Immunization Practices (ACIP) in 1998. This vaccine was evaluated in 18,000 infants in pre-licensing trials during which five cases of intussusception among 10,054 infants receiving vaccine and one case in 4,633 placebo patients (0.05% vs. 0.02%, P > .45) was reported. The vaccine was thus recommended for routine use in October 1998 for infants at age 2, 4, and six months. In July 1999, the Vaccine Adverse Event Reporting Systems (VAERS) reported 15 cases of intussusception among recipients. A subsequent control investigation demonstrated a strong relationship between RotaShield and intussusception, prompting withdrawal of recommendation for routine use in October 1999. The manufacturer voluntarily withdrew this product from the market shortly thereafter.

IV.d Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?

An AEFI investigation (through a detailed history, clinical examination and laboratory investigation in a patient) may unravel other intrinsic pre-existing illness, health conditions or risk factors that may have precipitated the AEFI. For example:

- An infant who is a known case of birth anoxia with seizure disorder has a seizure following vaccination that gets reported as an AEFI

IV.e Was this patient taking any medication prior to the vaccination?

Medications are known to cause adverse reactions and, when given concurrently with vaccine(s), must be considered as possible coincidental causes of an observed AEFI. For example

- Stevens-Johnson syndrome that has an onset 2 days after vaccination in an individual on a sulfa antibiotic could be a coincidental event (due to the sulfa drug) or a vaccine product-related reaction (due to the vaccine).

IV.f Was this patient exposed to a potential risk factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?

Prior exposure to extrinsic risk factors/toxins may be a clue to the possibility that an AEFI is a coincidental event. One should also consider the possibility of an interaction between a risk factor/toxin and vaccine in causing the AEFI.

For example:

- A patient who undergoes a surgical procedure a week prior to vaccination (with an apparently normal post-operative period), may present with fever a day after immunization. One needs to determine if the fever (which is an AEFI) is a coincidental event that occurred as a late complication of surgery or if it is due to the vaccine or vaccination process (product-related, quality defect-related, or immunization error-related).

- An example of exposure to a potential risk factor (other than vaccine) prior to the event could be a case of known peanut or other food allergy receiving a vaccine soon after getting exposed to the allergen (ingesting food containing peanuts) and reporting urticarial rash.

Table 8.1: The Causality Assessment Checklist

Step 2 (Event Checklist) √ (check) all boxes that apply					
I . Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	☐ Y	☐ N	☐ UK	☐ NA	
II. Is there a known causal association with the vaccine or vaccination? (Vaccine product)					
Vaccine Product					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event even if administered correctly?	☐ Y	☐ N	☐ UK	☐ NA	
2. Is there a biological plausibility that this vaccine could cause such an event? https://bit.ly/3ecoAI0	☐ Y	☐ N	☐ UK	☐ NA	
3. In this patient, did a specific test demonstrate the causal	☐ Y	☐ N	☐ UK	☐ NA	
Vaccine Quality					
4. Could the vaccine given to this patient have a quality defect	☐ Y	☐ N	☐ UK	☐ NA	
Immunization Error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (eg.use beyond the expiry date,wrong recipient etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐ Y	☐ N	☐ UK	☐ NA	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐ Y	☐ N	☐ UK	☐ NA	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)	☐ Y	☐ N	☐ UK	☐ NA	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
Imm. Anxiety- ITSR					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction. hyperventilation or anxiety)?	☐ Y	☐ N	☐ UK	☐ NA	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?					
12. In this patient, did the event occur within a plausible tme window after vaccine administration?	☐ Y	☐ N	☐ UK	☐ NA	
III. Is there strong evidence against a causal relationship ?					
1. Is there a body of published evidence (systematic reviews. GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event? https://bit.ly/3f8F1q6	☐ Y	☐ N	☐ UK	☐ NA	
IV. Other qualifying factors for classification					
1. In this patient. did such an event occur in the past after administration of a similar vaccine?	☐ Y	☐ N	☐ UK	☐ NA	
2. In this patient did such an event occur in the past independent of vaccination?	☐ Y	☐ N	☐ UK	☐ NA	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐ Y	☐ N	☐ UK	☐ NA	
4 Did this patient have an illness, pre-existing condition or risk factor that could have contribute to the event ?	☐ Y	☐ N	☐ UK	☐ NA	
5. Was this patient taking any medication prior to the vaccination?	☐ Y	☐ N	☐ UK	☐ NA	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐ Y	☐ N	☐ UK	☐ NA	

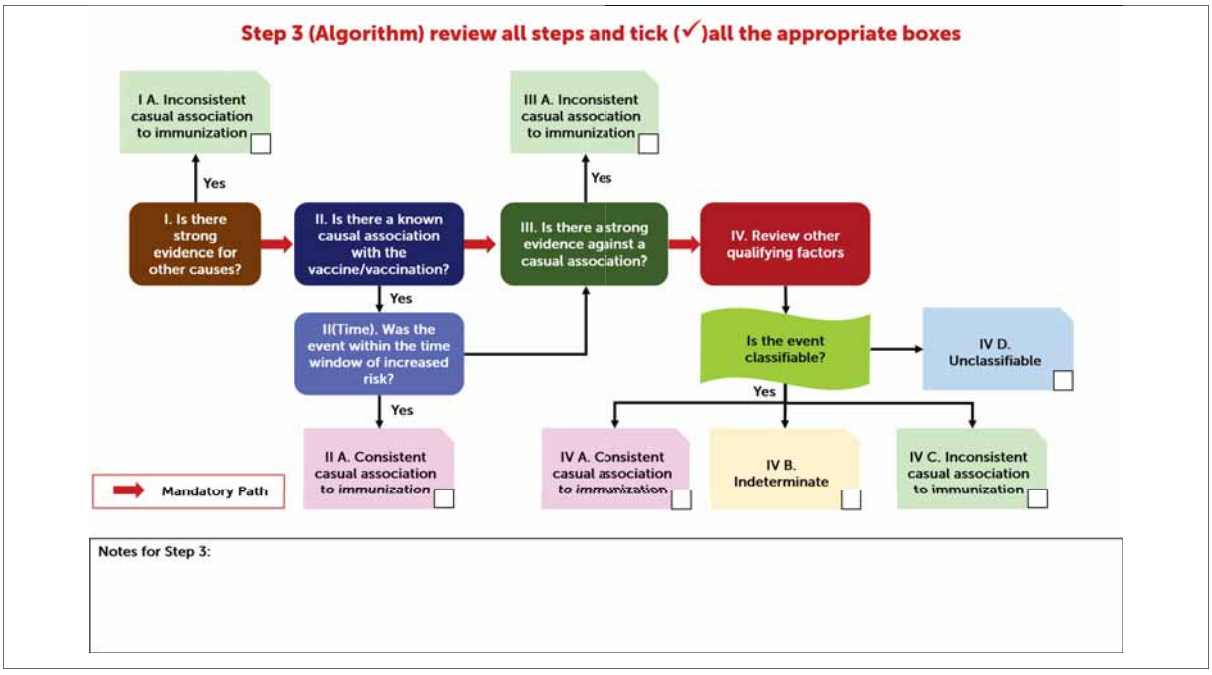
Y: Yes N: No UK: Unknown NA: Not applicable or Not available

Step 3: Algorithm

After the checklist is completed, data related to the association under investigation is ready to be applied to the algorithm. The algorithm aims to be a roadmap for decision-making by reviewers but it does not, and should not, take away the expert and deductive logical process inherent in linking a diagnosis to its potential cause. The stepwise approach of the algorithm helps to determine if the AEFI could be consistent or inconsistent with an association to immunization, indeterminate or unclassifiable (Figure 8.3).

The algorithm allows the reviewers to focus logically and document their observations to the appropriate conclusions. "Yes" responses in the checklist should have corresponding conclusions in the algorithm.

Figure 8.3: Causality Assessment - Algorithm



The boxes on the mandatory path correspond to the four major sections in the checklist (I to IV). It is essential that the reviewers evaluate all four boxes using the responses in the checklist. The conclusions are colour-coded green if the conclusion is inconsistent with a causal association to immunization; pink if it is consistent with a causal association to immunization; yellow if it is indeterminate; and blue if the event is unclassifiable.

The algorithm allows the reviewers to focus logically and document their observations to the appropriate conclusions. "Yes" responses in the checklist should have corresponding conclusions in the algorithm. The boxes on the mandatory path (red arrow) correspond to the four major sections in the checklist (I to IV). It is essential that the reviewers evaluate all four boxes using the responses in the checklist. The conclusions are colour-coded green if the conclusion is inconsistent with a causal association to immunization; pink if it is consistent with a causal association to immunization; yellow if it is indeterminate; and blue if the event is unclassifiable.

During the initial stages of the assessment when considering the eligibility (step 1), the reviewer may consider the available information to be sufficient for initiating the causality assessment process. However, after completing the checklist (step 2), it may be discovered that the information is insufficient to arrive at a definite conclusion. At this stage of the review, the reviewer may decide to categorize the case as "Unclassifiable" (check-box marked in blue in Fig 8.3) and specify the missing information that prevents the classification of the case.

Responses IA, IIA and IIIA have greater strength and these conclusions have greater weight. When the conclusion is "unclassifiable", the reviewers should determine the reasons and document why classification was not possible and all attempts should be made to obtain the necessary supporting evidence for classification.

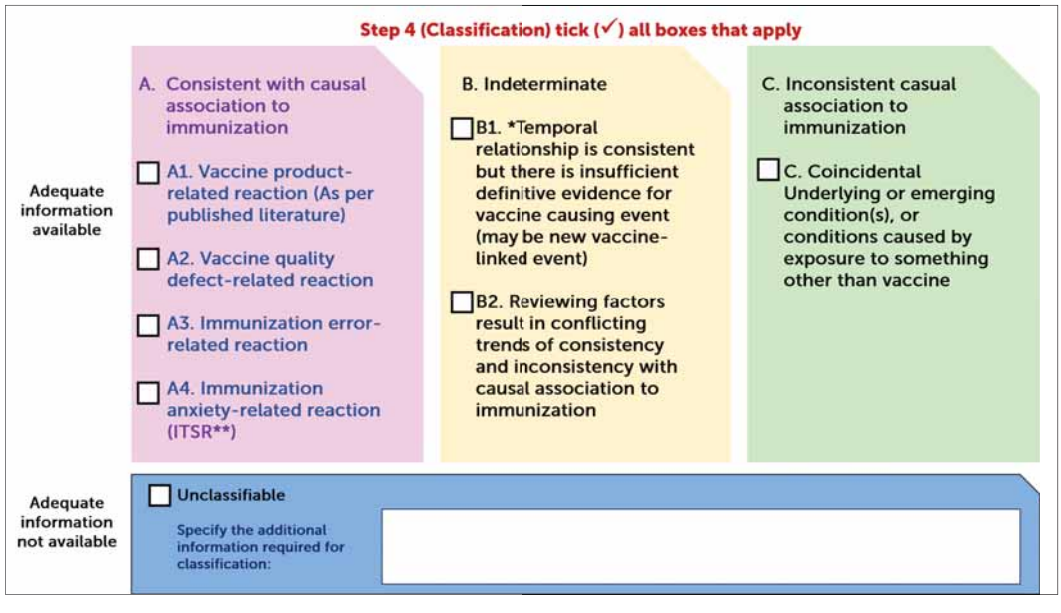
Notes for Step 3: A space has been given at the end of Step 3 to summarize the responses in the checklist adjacent to the corresponding conclusion and enable the assessors to have a transparent "dashboard view" of their conclusions and the logic for arriving at them.

For example, in a case of a febrile seizure occurring within 24 hours of pentavalent vaccine with whole cell pertussis component which has recovered without sequelae, the note can summarize that the whole cell pertussis vaccine is known to cause seizures within 24 hours of administration, there is a biological plausibility of this happening, there is no evidence of an alternate diagnosis and the child recovered without any sequelae.

Step 4: Classification

The final classification has been adapted from *Definition and application of terms for vaccine pharmacovigilance. Report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance*. The cause-specific definitions provide clarity on "A. Consistent causal association to immunization" and "C. Inconsistent causal association to immunization" (coincidental)". The association is considered "B. indeterminate" when adequate information on the AEFI is available but it is not possible to assign it to either of the above categories. The details are presented in Figure 8.4.

Figure 8.4: Causality Classification



The final classification is based on the availability of adequate information.

I. Case with adequate information for causality conclusion

A case with adequate information for causality conclusion can be classified as follows:

A. Consistent causal association to immunization

A1. Vaccine product-related reaction; or
A2. Vaccine quality defect-related reaction; or
A3. Immunization error-related reaction; or
A4. Immunization anxiety-related reaction.

B. Indeterminate

B1. Temporal relationship is consistent but there is insufficient definitive evidence that vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.
B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).

C. Inconsistent causal association to immunization (Coincidental)

This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine.

II. Case without adequate information for causality conclusion

As mentioned above, such cases are categorized as "unclassifiable" and require additional information for further review of causality. The available information on unclassifiable cases should be placed in a repository or an electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

8.4 Summarizing the Logic of AEFI Causality Assessment

Causality assessment is performed with the available information and resources that are at the reviewers' disposal at a given point in time. The information and resources may be adequate or inadequate. If a case that is initially evaluated as eligible for classification, but is found to have inadequate information when assessed, causality assessment is not possible and the case is categorised as unclassifiable. Even with adequate information, the precision of causality is largely determined by the quality of AEFI investigation and the expertise, experience and skill of the assessors.

It must be remembered that at the individual level it is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report. Different cases, when systematically reviewed, may reveal conflicting findings

that have to be debated by a group of experts before a clearer picture of causality emerges. It is possible that there may be more than one conclusion on causality by the same reviewers. The final decision on prioritizing the choices logically needs to be made after discussion and arriving at a consensus.

The categories "Consistent causal association to immunization" and "Inconsistent causal association to immunization" (coincidental) are clearly outlined in the *Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance*1 and are described in the next section. With available evidence, several cases would still be classified as "indeterminate" especially for the AEFIs reported after a new vaccine. This must be discussed by the assessment team to determine if this is a signal or if additional investigation or special tests are needed

Summary of Classification Logic

Summarize the classification logic in the order of priority:
With available evidence, we could conclude that the classification is _____because:

With available evidence, we could NOT classify the case because:_____

Causality can change when additional information becomes available either about the same case or about similar cases. For example, a case of narcolepsy after H1N1 influenza vaccine may currently be classified as a likely vaccine product related AEFI, while the same case would have been classified as coincidental or indeterminate prior to establishing the association between narcolepsy and influenza vaccine in 2010 by scientific evidence. Resource constraints such as non-availability of autopsy facilities and special laboratory tests (such as the tryptase test as an indicator of mast cell activation in anaphylaxis) can modify interpretations.

8.5 Underlying Mechanisms for AEFI Classification

A. Consistent Causal Association to Immunization

A1 and A2 Vaccine Product-Related and Vaccine Quality Defect-Related Reactions

Vaccines are designed to induce a response by the immune system which involves a complex interaction between the vaccine antigens, the adjuvant (if present), antigen-presenting cells, lymphocytes and multiple immune mediators (cytokines). This interaction is important to the development of the desired immunity against the specific vaccine-preventable disease. However, the immune response in a vaccinee may manifest as relatively common and mild adverse reactions to the vaccine(s), such as redness and swelling at the injection site, or fever. Homeostatic mechanisms usually limit the inflammatory response so that such reactions are short-lived and have no lasting consequence. Uncommonly, the immune response to one or more vaccine components may result in a longer-lasting and more severe adverse reaction. Rarely, the immune response may cause a life-threatening reaction.

It is important to note that vaccine product-related reactions may unmask a predisposition in certain high-risk individuals to other adverse events that would not occur in the majority

of vaccinees. For example, fever is a relatively common inflammatory response following vaccination. For most vaccinees the fever is of short duration and there are no associated adverse reactions. However, in children with an underlying seizure disorder, or in infants and toddlers with a tendency to have febrile seizures, the fever may trigger a seizure. Other events that cause fever, such as respiratory infection, could also trigger a seizure. In such cases, the seizures result from a combination of an inherent property of the vaccine that caused fever and underlying factors in the vaccinee that lowered the threshold for seizure associated with fever.

A.1 Vaccine product-related and A.2 Vaccine quality defect-related reactions: Vaccine product-related reactions are expected or known to occur vaccine reactions within a certain frequency and severity. If an event is reported beyond the expected frequency or severity, this could be because of A2. Vaccine quality defect-related reaction. Examples of vaccine product-related and vaccine quality defect-related reactions are as follows:

- Reactions associated with the route and/or site of administration of the vaccine product or vaccinee-specific characteristics. Examples are Bell's palsy following intranasal administration of intranasal influenza vaccine where the causative mechanism was attributed to the vaccine composition combined with the mode of administration (vaccine product-related reaction); or pain at the time of injection and associated physiological responses – which can be vaccine-product related if within the expected frequency and can be vaccine quality defect-related reaction if this event is seen in more than expected frequency.

- **Immune-Mediated Vaccine Reactions:**
  (a) Local reactions, with involvement of the injection site, due to one or more vaccine components can be immune mediated. Examples are extensive limb swelling after DPT vaccination (local inflammation, manifest as one or more of swelling, redness, pain, local tenderness and induration), aluminium adjuvant hypersensitivity and granulomatous inflammation at the injection site with or without regional lymphadenitis (most commonly related to BCG vaccine). Clustering of such events related to a particular manufacturer or a batch or reporting at higher than the expected frequency could indicate vaccine quality-defect related reaction.
  (b) Multisystem (generalized) reactions due to one or more vaccine components, i.e. systemic inflammatory response (e.g. fever or lethargy); mast cell degranulation - IgE mediated hypersensitivity (anaphylaxis) or non-IgE mediated hypersensitivity (reactions in this group are commonly referred to as anaphylactoid reactions), disseminated granulomatous reaction (e.g. disseminated BCG in immunodeficient hosts).
  (c) Organ-specific reactions due to one or more vaccine components, i.e. auto-immune or undefined mechanism - central nervous system (e.g. demyelinating conditions such as GBS post-influenza vaccination), blood (e.g. thrombocytopenia post-MMR vaccination), skin (e.g. rashes after vaccination, including urticarial).

- Reactions as a consequence of replication of vaccine-associated microbial agent(s) in the vaccinee or in a close contact of the vaccinee. The microbial agent(s) could be an attenuated vaccine agent (vaccine product related reaction); a wild-type vaccine agent due to insufficient inactivation during the manufacturing process (vaccine quality defect related reaction); a contaminant introduced into vaccine during the manufacturing process (vaccine quality defect related reaction).

A3. Immunization Error-Related Reaction

The emphasis for AEFI in this category is their preventable nature. Thus, the classification mechanism focuses on the nature of the error rather than on the biological process(es) giving rise to the specific AEFI.

Immunization error-related reactions are described below:

1. Error in vaccine handling - exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent), resulting in inactivation of active vaccine components leading to failure to cause adequate immune response; systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines; use of a product after the expiry date, resulting in failure to cause adequate immune response as a result of loss of potency or non-viability of an attenuated product.

2. Error in vaccine prescribing or non-adherence to recommendations for use:
   (a) Failure to adhere to a contraindication, resulting in:
      (i) Anaphylaxis following administration of a vaccine to an individual known to have an immune-mediated hypersensitivity to one or more components
      (ii) Disseminated infection with an attenuated live vaccine agent following administration to an individual with a known immunodeficiency that contraindicated use of any live vaccines
      (iii) Vaccine-associated paralytic polio in an immunocompromised household contact of a child given oral polio vaccine;
   (b) Failure to consider appropriately warnings or precautions for vaccine use- for example, adenitis following subcutaneous BCG vaccination instead of intradermal route;
   (c) Failure to adhere to vaccine indications or prescription (dose or schedule), resulting in:
      (i) Systemic and/or local reactions following administration of an incorrect dose or wrong product or administration to an individual in an incorrect age group
      (ii) Neurological, muscular, vascular or bone injury due to incorrect injection site, equipment or technique.

3. Error in Administration:
   (a) Use of an incorrect diluent or injection of a product other than the intended vaccine, resulting in failure to vaccinate due to incorrect diluent or reaction due to inherent properties of whatever was administered other than the intended vaccine or diluent;

(b) Incorrect sterile technique or inappropriate procedure with a multidose vial, resulting in infection at the site of injection due to a microbial contaminant introduced during administration of the vaccine or infection beyond the site of injection due to a microbial contaminant introduced during administration of the vaccine (e.g. toxic shock syndrome);

(c) Inadvertent administration of vaccine to someone for whom it was not intended (e.g. via a needlestick injury or splash to the eye depending on the vaccinee characteristics).

A4. Immunization Anxiety-Related Reaction (Immunization Triggered Stress Response - ITSR)

Stress responses to immunization can be triggered and may manifest just prior to, during, or after immunization. It is called Immunization Triggered Stress Response (ITSR). ITSR can be broadly classified as:

- Peri-immunization stress responses where symptoms may manifest immediately before, during, or after immunization. Unlike other classifications of AEFIs that always present post-immunization, peri-immunization ITSR may even occur prior to immunization in anticipation of the procedure. Peri-immunization stress responses are usually immediate, transient and resolve spontaneously.
- Post-immunization stress responses may or may not be preceded by a peri-immunization ITSR. The symptoms and signs may take many hours to days to develop. Longer-lasting responses may involve increased sensitivity of the Hypothalamic Pituitary Adrenocortical axis.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

In this case, the temporal relationship is consistent but there is insufficient definitive evidence for the vaccine causing the event (it may be a new vaccine-linked event). The details of such AEFI cases should be maintained in a national database. Over time, as more doses of the same or similar vaccines are administered and if similar events are reported from one or multiple sources, the recorded cases will help to identify a signal suggesting a new potential causal association, or a new aspect of a known association, between the vaccine and the event.

In late 2010, doctors specializing in sleep disorders in Finland and Sweden reported an increase in reporting of cases of narcolepsy especially in children and young adults following the use of Pandemrix, a vaccine against influenza (H1N1) 2009. Studies conducted in early 2011 in both countries suggested an increased risk of narcolepsy following vaccination with Pandemrix. Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. It has a strong genetic linkage, being almost uniquely seen in persons who have the (HLA) DQB1*0602 genotype. It was considered that the vaccine increased the risk of narcolepsy in a joint effect in those genetically disposed with some other, still unknown, genetic and/or environmental factors. While temporal association was strong and epidemiological studies also indicated an increased risk of narcolepsy following vaccination with Pandemrix, definitive evidence

for the vaccine causing the event was not available. The countries continued to use the Pandemrix vaccine till stocks were exhausted. The manufacturer did not apply for renewal of license to market the vaccine citing lack of demand for the vaccine.

Reporting of AEFIs after COVID-19 vaccination saw several conditions being reported. These were classified as B1 initially. Over time, thrombotic thrombocytopenia syndrome (TTS) was found to be causally linked to COVID-19 vaccine, and thus subsequently diagnosed cases of TTS were classified as having A1 causality classification. Several other AEFIs for example myocarditis and GB Syndrome are still considered as having B1 classification, with not enough evidence at present to establish a causal relation between COVID-19 vaccine and these conditions.

B2. Conflicting trends of consistency and inconsistency with causality

Reviewing factors may result in conflicting trends of consistency and inconsistency with causal association to immunization. Even with adequate information, these AEFI cases cannot be clearly categorized because the outcomes of investigation may give contradictory conclusions. There could be clear pointers indicating that the event is related to the vaccine or the vaccination and at the same time there could also be clear evidence that some other factor may be responsible. An example of this would be a report of encephalitis following administration of JE live attenuated vaccine in a JE endemic region during the transmission season.

C. Inconsistent Causal Association to Immunization (Coincidental)

AEFI can result from underlying or emerging conditions of the vaccinee as well as from external exposures that can cause harm independent of immunization. These include, but are not limited to, the following:

Underlying or emerging condition(s) in the vaccinee

Such underlying or emerging conditions could include:

- manifestation or complication of a congenital or inherited underlying disease condition or birth injury; or an underlying acquired disease condition that may or may not have been diagnosed prior to immunization; psychogenic illness.

Conditions caused by exposure to external factors

Conditions caused by factors other than vaccine could include

- infections due to bacteria, viruses, fungi or parasites;
- adverse reaction due to recent or concomitant medication;
- allergic and other hypersensitivity reactions due to exposure to allergens other than those present in the vaccine;
- injury due to exposure to environmental toxins; trauma, including surgery.

An example of this is an infant reporting with seizure after receiving pentavalent vaccine and cerebrospinal fluid examination indicating meningitis.

AEFI Causality Assessment Software

An e-tool for AEFI causality assessment has been developed which takes the assessor through the four steps of the causality assessment: (1) causality question framing; (2) checklist; (3) algorithm and (4) classification. The responses to the questions in the checklist are to be marked in the software. For the responses marked as 'yes', the rationale/ justification for the response should be mentioned. Based on the responses, the software algorithm suggests the possible pathways, followed by the suggestion of classification. The assessor can select the most suitable classification and justify the same. The causality assessment software can be accessed at https://gvsi-aefi-tools.org/ for use in both online and offline modes.

8.6 Initiating action after AEFI Causality Assessment

Determining causality is not an end in itself. The lessons learned from the assessment should provide insights and guidance for the technical, immunization programme and administrative managers on the causes and the logical next steps – including training, research, modifying systems, refining tools and so on – to avoid and/or minimize recurrences. Duly approved standard protocols need to be established for responding to AEFIs. Some recommended actions at district, state and national level for different causality assessment results are as follows:

A. Consistent Causal Association to Immunization

A1. Vaccine Product-Related Reaction

Details of cases classified as vaccine product-related reactions in the national database will be analysed regularly for unusual increases. The frequency of reporting of certain events (observed rates) will also be compared with available background (expected) rates. Any increase in the observed rates should trigger an assessment to identify the reason and take appropriate action.

Action for A1: Vaccine Product-Related Reaction

National level: If a periodic review of antigen-event pairs (batch-wise, manufacturer-wise, vaccine-wise) indicates a more than-expected reporting or frequency of events exceeding the background rate, the NRA should be informed. Stimulated/active surveillance or studies to investigate further may be recommended. The information and advice for future vaccination or care should be provided to health care providers and the community as appropriate.

State level: A more than usual reporting of antigen-event pairs should be informed to the national level/state regulatory body for further actions.

A2. Vaccine Quality defect-Related Reaction

If a reaction is related to a particular lot or batch, the distribution of the lot or batch has to be ascertained and specific instructions must be provided on the utilization or non-utilization of the lot or batch. It is important to inform the national regulatory authority and the marketing authorization holder about the AEFI.

Action for A2 – Vaccine Quality Defect Related Reaction

National level: Perform periodic review of antigen-event pairs (batch-wise, manufacturer-wise, vaccine-wise) for more than expected reporting as compared to background rate. NRA should be informed for appropriate regulatory actions. Stimulated/active surveillance or studies for further investigations may be recommended.

State level: Perform periodic review of antigen-event pairs (batch-wise, manufacturer-wise, vaccine-wise) for more than expected reporting as compared to background rate. Assess, inform national / state regulatory body for further actions.

A3. Immunization Error-Related Reaction

Training and capacity-building are critical to avoid recurrences of such reactions.

Action for A3 – Immunization Error Related Reaction

National and state levels: Recommend corrective action – identifying the cause, training, increased supervision, change in guidelines, etc.

State and District - Identify the cause, conduct trainings, increase supervision, implement changes in guidelines, etc.

A4. Immunization Anxiety-Related Reaction (Immunization Triggered Stress Response - ITSR)

Depending on the nature of the ITSR (solitary or in a cluster), there are different approaches for prevention, diagnosis and management including communications, training and capacity-building and improvement in the environment in which immunization is carried out, to avoid recurrences of such reactions.

Action for A4 – Immunization Anxiety Related Reaction (Immunization Triggered Stress Response – ITSR)

National and state levels: SOPs to help reduce the chances of anxiety-related reactions during immunization sessions should be included in immunization guidelines and training modules. This is particularly important when mass immunization campaigns are being planned. Vaccinators should be trained to be alert for signs of anxiety and fear around vaccination and take appropriate action.

District: Vaccinations should be conducted in a well-ventilated room with no crowding. Vaccinators should explain the procedure to each beneficiary before the process and reassure them that pain will be minimal. The vaccinator should be alert to detect early signs of anxiety before the vaccination procedure. Vaccinations should be conducted in a manner such that persons waiting for vaccinations do not witness the process when conducted on others. A person who clearly expresses anxiety should be vaccinated first, in a lying down position and should remain in that position for at least 10 minutes under watch. After vaccination, all beneficiaries should be under observation for 30 minutes.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

The details of such AEFI cases should be maintained in a national database. Later this can help to identify a signal suggesting a new potential causal association, or a new aspect of a known association, between a vaccine and an event or set of related events.

Action for B1: Indeterminate-Temporal Relationship Exists, Insufficient Evidence for Causality

National: Regular review of the database for identification of possible signals for further assessments as per signal management protocol should be done.

B2. Conflicting trends of consistency and inconsistency with causality

Action for B2: Indeterminate - Conflicting Trends of Consistency and Inconsistency with Causality

National: These cases are classified on the basis of available evidence. If additional information becomes available, the classification can move into a more definitive category. During the assessment, the reviewers should clarify what additional information would be helpful to finalize the causality assessment and should seek information and expertise from national or international resources.

C. Inconsistent Causal Association to Immunization (Coincidental)

Action for C. Inconsistent causal association to immunization (coincidental)

The information should be provided to patients, their relatives, the care provider and the community.

D. Ineligible Cases and Unclassifiable Cases

For both ineligible and unclassifiable cases, it is important to specify the missing elements and make attempts to obtain the information so that causality assessment can be attempted again. The state AEFI committee should review the causes of cases being ineligible for causality assessment and track it as an indicator to reduce it for the state.

One of the reasons for the large number of unclassifiable cases may be related to the quality of investigations. Feedback should be given to districts when cases are unclassifiable because of poor quality of investigations. Trainings at the state level can focus on improving the quality of investigations. The receipt of additional information should lead to a reassessment of causality by the trained assessors.

Action for D: Unclassifiable Cases

National and state levels - Identification of crucial missing information which would help to give a valid diagnosis or to classify and requesting district to provide the information.
District - Get the required information and share with the state/national levels for assigning diagnosis and classifying the case. Training of the investigation team.

Action for Ineligible cases

National and state levels - Identification of crucial missing report/record related to the case leading to a valid diagnosis or to classify and requesting district/state to provide the record/report.
District - Complete the investigation and get the required record/report and share with the state/national levels. Conduct training of the investigation teams.

8.7 Causality Assessment: State Level Operational Aspects

It is the responsibility of the state AEFI committee to conduct causality assessments of reported AEFI cases and share the approved causality assessment results with the national level within 90 days of notification of the case. There may be several challenges to the timely completion of causality assessment. These may include a large number of AEFI cases reported, delayed/incomplete case investigation, a large backlog and sometimes a lack of trained experts or support in the SEPIO office for causality assessment.

8.7.1 Screening of Cases and Other Steps to be Taken Before a Causality Assessment

Prior to causality assessment, all cases should be screened by the state immunization office or the technical collaborating centre by persons trained in (or familiar with) the causality assessment process. The objective of the screening process is to ensure that there are maximum chances of cases going beyond Step 1 (eligibility) of the causality assessment process by ensuring that the four pre-requisites of Step 1 of causality assessment is fulfilled during the screening process. This saves time of the experts and makes the causality assessment process more efficient.

During state AEFI committee meetings held for discussing and approving the results of the causality assessments of cases, the committee members should be informed of the proportion of cases incomplete for causality assessment and the steps taken to ensure completeness. A timeline may be given to districts, within which necessary case records/reports/information should be provided by the districts to render the cases as complete for causality assessment. The record, information or clarification once received should be included in the case records.

Screening of cases before causality assessment will help identify:

1. Cases which have been investigated but supporting documents/information are not available: Districts should be informed that the specific supporting documents/information should be shared within a specific timeline to enable early causality assessment.

2. Cases which have all reports and supporting documents but specific clarifications are required to ensure informed causality assessment: Districts should be asked to provide clarifications within a specific timeline to enable early causality assessment.
3. Clusters: Ensure documents pertaining to all cases belonging to the cluster are available so that causality assessment of the cluster is done together. A summary of the cluster with brief information of each case belonging to the cluster will help to ensure all information is available for conducting causality assessment.

CRF and CIF are the basic documents required for all serious / severe AEFI cases. If the case was hospitalized, hospital records till the time of discharge/death including the final diagnosis and discharge slip are important for causality assessment. Usually, laboratory test reports are part of the hospital records. However, some reports may be received after the discharge of the patient from the hospital or some tests may be done after the patient in discharged. For example, EEG may be done after the child is discharged from hospital and this may be crucial for an informed causality. Some AEFI cases might also have been reported to the AFP surveillance system. In such cases, stool sample test reports should also be included in the case records.

In case of deaths, post-mortem reports are important. While gross reports are usually available relatively quickly, viscera reports are often delayed. It is important to follow up for these reports and not conduct the causality assessment without them unless it is very clear that the reports may not be received as the viscera has not been sent for histopathological examination/ toxicology, or the gross post-mortem examination clearly provides a cause of death. In case of all deaths, verbal autopsies must be conducted. During the screening process for all deaths, the availability of the verbal autopsy should be checked. If crucial information is missing or there are discrepancies in the verbal autopsy report, the district may be asked for clarifications or to provide the missing information if available. If vaccine samples or samples of syringes have been sent for testing to CDL Kasauli or CDL Kolkata, the report of these tests should also be part of the case records for causality assessment to be conducted.

At the end of the screening process, a case ready for causality assessment (Step 1) will have a:

1. CRF with details of vaccine/s administered and preliminary diagnosis/signs/symptoms
2. CIF with all sections filled, including the final diagnosis (or signs/symptoms) and outcome
3. Hospitalised cases- complete hospital records till discharge with all laboratory reports and clear outcome (recovered completely and discharged/recovered with sequelae and discharged/died)
4. Death cases –
   (a) Fill verbal autopsy form in all death cases even if post-mortem has been conducted
   (b) If post-mortem has been conducted – preliminary post-mortem report, histopathology and/or chemical analysis report (if viscera sent for HPE and chemical/toxicology tests) and final cause of death report.
5. Cluster cases – A summary of the cluster with brief information about each case.

8.7.2 Conducting Causality Assessment Meetings

The following models are proposed to states to enable them to conduct timely causality assessments:

Model 1: If the case load for causality assessment is less, the cases may be assessed by the members of the state AEFI committee in its regular meetings held quarterly or more frequently, if required.

Model 2: States reporting a larger number of cases may form a causality assessment sub-committee at the state level with the required trained experts which meets more frequently for conducting causality assessments.

Model 3: States can also form more than one causality assessment sub-committees at the regional level (covering a group of districts/urban areas). These regional sub-committees can conduct causality assessments for cases reported from their respective regions.

In models 2 and 3, a summary of the causality assessment results may be presented by the chairperson of the sub-committee to the state AEFI committee. The few specific cases of interest or requiring inputs of the experts of the state AEFI committee may also be discussed in the state AEFI committee meetings. The cases for discussion could be deaths, those classified as indeterminate/unclassifiable and cluster AEFI. After the causality results are approved by the state AEFI committee, the results will be shared with the national level.

It is important to ensure that all the experts performing causality assessment in sub-committees/ state AEFI committee are trained (either at the national or state level trainings), with very clear terms of reference formally communicated to them. A state AEFI committee representative may be present in causality assessment sub-committee meetings for facilitation and monitoring of quality.

To ensure unbiased and independent assessments, the state EPI officer should ideally be not involved in causality assessments. However, s/he should ensure that all investigation forms, reports and case records for reported AEFI cases are received on time and meetings are held as planned, for causality assessments to be completed and approved by the state AEFI committee within the stipulated timelines. The SEPIO should facilitate the presence of district immunization officers in the state AEFI committee meetings (if required) during the causality assessment to provide missing or additional information when cases from the district are being causally assessed.

It is desirable that the SEPIO should identify a medical college to function as a State AEFI Technical Collaborating Centre. State AEFI committee meetings and causality assessment meetings can be held in the state AEFI technical collaborating centre. Experts from other medical colleges can also be members of the state AEFI Committee and/or causality assessment sub-committee.

Once approved by the state AEFI committee, the completed Causality Assessment Form (**Annexure 14A**) should be uploaded on SAFE-VAC. The causality assessment report should include diagnosis and classification, and should be signed by members conducting the causality assessment. It should also include remarks/inputs of the State AEFI committee for the district AEFI committee or the district immunization programme manager.

8.8 Causality Assessment: National Level Operational Aspects

Causality assessment is also conducted at the national level by the AEFI secretariat . Currently, the results of the causality assessment done at the national level are considered as final. The model being followed at the national level is model 2, wherein there is a sub-committee at the national level which classifies all the reported serious and severe cases in the country. A summary of these cases along with details of cases that need further discussion are presented to the National AEFI Committee, It may be noted that the sub-committee meetings at the national level are held more frequently and the National AEFI Committee meetings are held on a quarterly basis. The Causality assessment form used at the national level is given in **Annexure 14B**.

Summary

- Causality assessment is the systematic evaluation of the information obtained about an adverse event following an immunization to determine the likelihood that the event might have been caused by the vaccine(s) received or vaccination process.
- Quality of investigations and adequacy and relevance of clinical, epidemiological and circumstantial information is crucial for informed causality assessment.
- A valid diagnosis is arrived at after considering all clinical details, review of child's environment, both within and outside the family, socio-cultural practices of the community, and epidemiological investigation.
- During the causality assessment process, after ensuring that the minimum criteria for causality assessment eligibility has been achieved, trained assessors use a checklist to identify factors that could have caused the event, recognize a pattern through an algorithm and finally apply the human element in ascertaining causality.
- As much as possible, evidences and logical reasons to justify the choice of response while navigating the algorithm, classifying the case and summarizing the logic should be recorded. The underlying mechanism for classification of AEFI cases needs to be well understood to assign classification.
- After conducting causality assessments, actions are taken to ensure preventable AEFIs do not recur and database of cases are systematically and regularly analysed to look for signals and ensure vaccines are safe.
- Operational aspects should be considered carefully to ensure efficiency of causality assessment processes at state and national levels to reduce ineligible cases and complete causality assessments within the recommended timeline for corrective action.

9 Operational Aspects of AEFI Surveillance

An effective immunization safety surveillance system must be able to timely detect and conclusively classify AEFIs to prevent their occurrence and/or reduce their impact. The surveillance of Adverse Events Following Immunization in India was first initiated in 1988-89.

9.1 Goal and Objectives of AEFI Surveillance

The overall goal of AEFI surveillance is to ensure that vaccines are administered safely with high levels of confidence and trust of public.

The specific objectives of AEFI surveillance are to:

- Timely detect, report and respond to AEFI
- Identify programmatic errors and implement corrective measures efficiently
- Document and promptly communicate any AEFI due to vaccine quality defect for regulatory action
- Document the rates of AEFI for a specific vaccine lot/brand in a specific region/population
- Estimate serious AEFI rates in the population and compare these with local and global data
- Identify signals of unexpected adverse events that would need further systematic analysis and/or planned studies to generate new hypotheses about such events.
- Sustain confidence of the public, health functionaries and professionals on the vaccines and immunization program

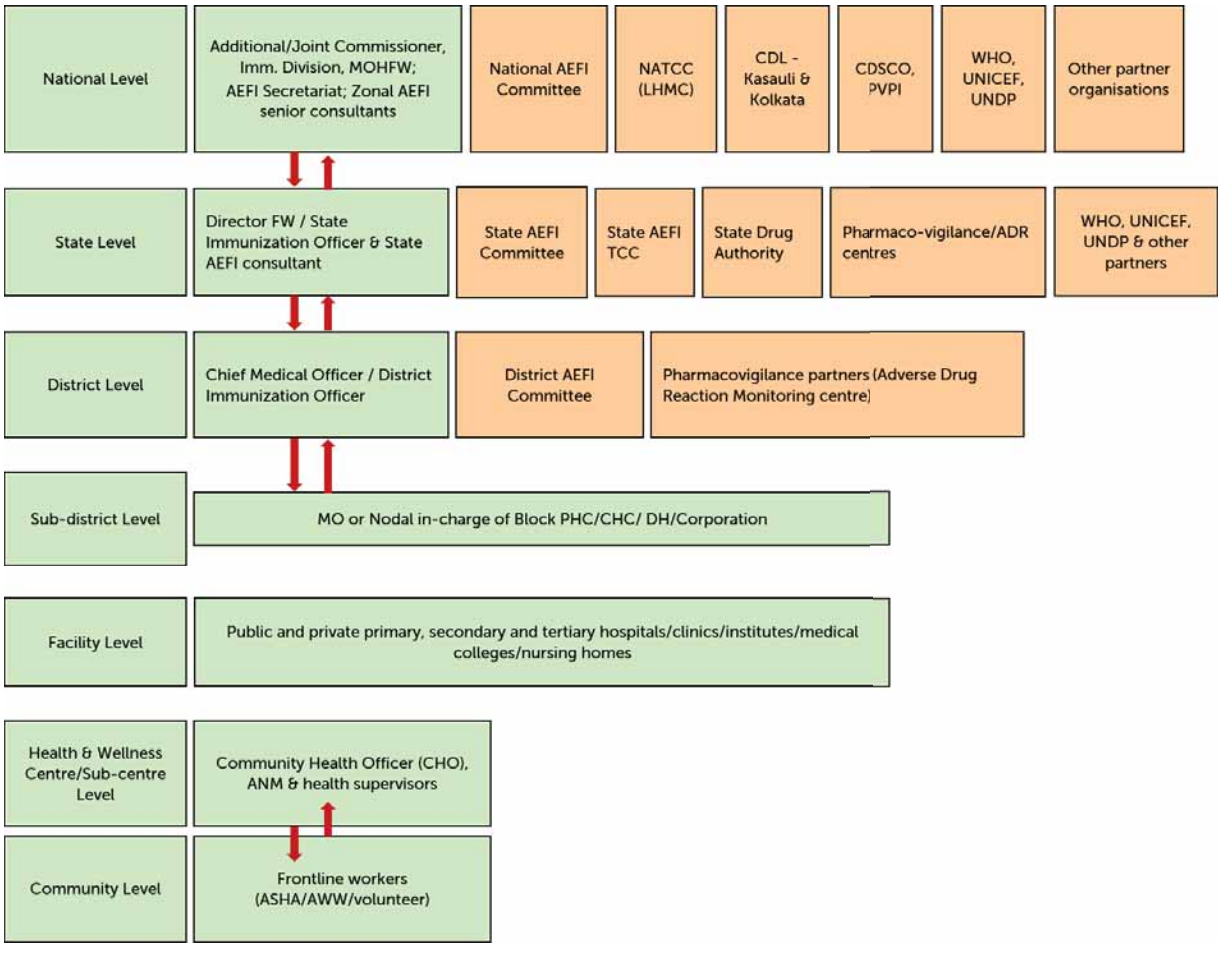
9.2 Key Activities of the AEFI Surveillance System

The AEFI surveillance system comprises of the following activities:

- Ensure prompt notification and reporting, rapid investigations and evaluation of AEFIs followed by effective response
- Build the capacity of various stakeholders at national/state/district level for strengthening of AEFI surveillance
- Conduct causality assessment at state and national levels and communicating causality results to state/district level programme managers
- Signal detection to assess any previously undocumented/unusual rates of AEFI related to a specific vaccine, a specific lot, or a specific brand
- Communication related to vaccine safety surveillance and responding to AEFI crisis.
- Convergence and sharing of information with regulatory and pharmacovigilance partners
- Regular monitoring and feedback to states for programmatic actions
- Use of information technology such as U-WIN for ease of reporting and electronic database (SAFE-VAC) for seamless investigation and analysis of AEFI cases at appropriate levels
- Formulation of well-defined standard operational procedures to ensure clarity, uniformity and avoid duplication of efforts to undertake all the above-mentioned functions.

The key players of the AEFI surveillance system are given in Figure 9.1.

Figure 9.1: Key Players of the AEFI Surveillance System



9.3 Roles and Responsibilities of Key Players

9.3.1 Community Level

ASHA & Anganwadi workers/volunteers /frontline workers

- After the vaccination session, use the beneficiary due list cum tally sheet to follow up beneficiaries for any suspected AEFIs or illness or problem after immunisation which requires a visit to a doctor or hospitalisation.
- Immediately inform the ANM, MO by telephone about the AEFI.
- Help the affected beneficiary access medical care by arranging referral transport.
- Assist the team investigating the event.
- Support in sustaining confidence of the community in vaccines and vaccination.

9.3.2 Sub-centre level

The roles of ANM and Health Supervisor have been described in sections below.

ANM

The ANM has key role in the prevention and management of AEFIs (refer Table 9.1).

Table 9.1: Key Role of ANM in AEFIs Prevention and Management

ANMs can help prevent AEFIs by:	ANMs can help manage AEFI by:
Following best immunization practices: • Ensure that the correct vaccines and diluents within expiry dates and usable VVM have been supplied by noting the following particulars, before starting vaccination at the immunization session site: » Manufacturer name » Batch number » Expiry date » VVM status (for new and partially used vaccines) » Date on the label of partially used vaccine (for vaccines under Open Vial Policy) » Date of expiry of other logistics such as contents of Anaphylaxis kit, Syrup Paracetamol, Syrup Vitamin A • Ensure that vaccine septum/label has not been submerged in water or contaminated in any way • Ensure four key messages are delivered and parents are reassured about the benefits of vaccination. Also, share the contact detail of AEFI management centre in case of any emergency. • Ensure that one bottle of syrup paracetamol (strength 125mg/5 ml) is dispensed to all the children who have been administered pentavalent or DPT in the session. ANM should explain the dosage and instruct the care-giver to administer syrup paracetamol to the child only when fever (axillary temperature > 38°C/100.4°F or child feels hot to touch) occurs after vaccination.	• Identifying initial signs of anaphylaxis and administer a single age-appropriate dose of injection adrenaline intramuscularly in suspected cases (**Annexure 5**). • Request AWW/ASHA to be alert, follow up and report AEFIs (if any) to her and the concerned MO. • Treat minor AEFIs (mild symptoms like fever, pain etc) symptomatically. • Provide immediate first aid to all other cases (serious/severe) and refer AEFI cases to MO (PHC) or to an AEFI management centre (nearest health facility with a medical officer) for prompt treatment. Inform the MO (PHC) at the health centre immediately by fastest means possible. • Share details of all AEFIs (serious/severe and non-serious) with the MO I/C in the weekly block level meeting. Ensure details of all serious/severe and minor cases are entered in the AEFI register maintained at the block PHC • Assist in investigation of AEFIs and take corrective action in response to the guidance from the MO (PHC).

During an immunization session, the following four key messages are to be communicated correctly to vaccine recipients and their relatives - the name of the vaccines administered and the diseases they will protect against; expected minor adverse events, their management and what to do in case of severe adverse events; the need to keep the vaccination card safely and bring it on the next visit; and when to come for the next vaccination.

Health Supervisors (HS)

- The Health Supervisors should supervise and provide hands-on training to the ANMs/ vaccinators in the field. The HS should focus on ensuring that the vaccinator is following correct injection practices, conveying the correct messages to parents and guardians and know how to arrange for referral transport and how to inform concerned officials in case of a crisis at the session site.
- To check for the availability of all vaccine and logistics such as anaphylaxis kit, syrup Paracetamol etc. Supervisor should also check for the expiry date of injection adrenaline available in the anaphylaxis kit.
- Monitor the immunization session/ANM if they are following recommended practices.
- Monitor the community for adverse events during their supervisory visits to immunization sites or sub-centres and liaison with community leaders to ensure their participation and confidence in the immunization programme. Also monitor and ensure follow-up of beneficiaries by health workers. Ensure reasons for dropout are entered in the counterfoils.
- Encourage health workers to report AEFIs. The serious/severe AEFIs should be notified immediately by fastest means possible.
- Analyse the reported AEFIs in the sub-centre reports and keep track of Health Workers who have not reported any AEFI over a period of time.
- Assist the investigation team in conducting the investigation and support with all possible/ available information at the centre and community level.

9.3.3. Facility Level

- All facilities (primary, secondary and tertiary care hospitals/medical college/nursing homes/clinics) in government and private sector should be included in the AEFI surveillance network. The primary responsibility for this activity lies with the DIO.
- The DIO, in consultation with the authorities of the facility, will identify and designate a nodal person for reporting of suspected AEFI cases. The nodal person could be medical officer or any other healthcare personnel of the institute such as a nurse, paramedical staff, resident medical officer etc.
- In large hospitals and medical colleges, personnel from various departments need to be oriented. These must include departments of Paediatrics and Community Medicine. Sensitisation of personnel from other departments including Medicine, Obstetrics and Gynaecology, Cardiology, Neurology, Paediatric Surgery, General Surgery, Dermatology, Forensic Medicine and Pharmacology is also desirable.
- The nodal person and other healthcare personnel of the concerned departments should be oriented to suspect and detect the AEFIs and report and manage them appropriately.
- An AEFI register should be maintained in these health facilities to record all AEFIs. The serious and severe AEFIs should be informed to the DIO immediately. For this purpose,

blank Case Reporting Forms should be available at the facility level with the nodal officer.

- The personnel in the facilities should also assist in the investigation and information collection for causality assessment of AEFIs and subsequent action.
- Special emphasis should be given for the referral hospitals and medical colleges as many of the sick infants and children are likely to attend the OPD or get admitted at the medical colleges and referral hospitals for serious/severe AEFI.
- Support should be taken from the Surveillance Medical Officer of WHO-NPSN network or AEFI consultants to sensitize and establish an AEFI reporting system in medical colleges and other such health facilities.

Involving Private Sector Doctors in Reporting of AEFIs

The private sector in India plays an important role in providing immunization services. The private sector helps to improve access to basic vaccines by filling gaps in service delivery due to flexibility in timings and approachability. Many private practitioners provide UIP vaccines through their clinics charging a small amount as vaccine administration charges. This makes it cost effective for vaccine beneficiaries who are accessing immunization services in the private sector.

Without the participation of private hospitals and clinics, the AEFI surveillance cannot be complete and comprehensive. Private sector reporting will provide safety data for newer and non-UIP vaccines which are given primarily in private sector. The private practitioners should be encouraged to report AEFI to the nearest government health care facility or the district immunization officer. AEFI surveillance can be improved through advocacy of professional organizations such as IAP, API and IMA. The Surveillance Medical Officer of NPSN can play a critical role in advocacy for reporting of AEFIs from private practitioners.

Registered members of the IAP can report any serious/severe case through the IAP app or through an online software at www.idsurv.org . Any private practitioner can report an AEFI by contacting the concerned DIO.

9.3.4 Sub-District (Planning Unit) Level

The planning unit for immunization programme will be the block PHC/ CHC or corporation. Sometimes, the district hospital also acts as a planning unit for the district headquarters. The role of a Medical Officer in charge of a planning unit at sub-district level (whether urban or rural) is in three broad areas:

1. Detection of AEFIs
2. Management of AEFIs
3. Reporting of AEFIs
4. Implementation of quality management system for AEFIs

1. Detection of AEFIs

- Train staff in detecting, managing and notifying all AEFIs and differentiating between minor and serious/severe events.
- Encourage staff to immediately report serious/severe AEFI.
- Confirm the information received from front line worker regarding suspected serious/ severe AEFI case

- During case visit, enquire about any recent outbreak of disease/illness or any death in the community which may or may not have been related to vaccination.

2. Management of AEFIs

- Clinical case management of AEFI and referral to next level if required

3. Reporting of AEFIs

- Ensure reporting of all serious/severe AEFIs occurring in the PHC area to the DIO within 24 hours of notification.
- Encourage recording of even minor events from all sub-centres and review during the weekly and monthly meetings.
- Ensure timely notification of AEFIs from sub-centre to PHC. Ascertain that ANMs provide details of all serious, severe and minor AEFIs in her area on a weekly basis.
- Verify the case entries done by the ANM and sign after the last case is recorded for the week. In case no AEFI (minor, severe or serious) case is identified and recorded in the AEFI register in a specific week, the MO will mention 'No case reported' and sign.
- Analyse the case entries (minor, severe and serious AEFI cases) on a monthly basis so as to identify any incidence of increased reporting with regard to an antigen, or suspected immunization error etc. The findings of this analysis should be shared with the DIO on a monthly basis.
- Ensure availability of blank CRF (at least 5 copies) at the planning unit so as to fill in the details of the notified serious/severe AEFI case and submit the same to the DIO within 24 hours.
- Maintain quality of AEFI case investigation and documentation (such as good clinical history, pre and post-vaccination health status, community investigation, etc).
- Collect all relevant records including hospital records (including OPD/IPD records, laboratory records, and other reports) of all the serious/severe AEFI reported and submit them to DIO.
- Track and collect post-mortem reports, histopathological reports, toxicology reports and final cause of death reports in AEFI death cases in which post-mortem has been conducted and submitted to DIO.
- In case of programme errors (e.g., abscess), the MO in-charge should try to find out the possible reasons and take corrective actions for the same.
- Actively help the district AEFI committee and the DIO in investigations, communicate findings to the vaccinators and health supervisors and share the results of the final causality assessment wherever possible after the confirmation from SIO/DIO.

4. Analysis of AEFI recording register

It is important for the medical officer at the PHC/CHC to analyze the trend of all types of AEFI cases (minor, severe and serious) documented in the AEFI recording register by the ANMs (Table 9.2).

Table 9.2: AEFI Register Sample Page

Week No.	Name of sub-centre	Name of vaccine recepient	Father's name	Age	Date of vaccination	Name of vaccines given	Batch number of vaccines	AEFI noted (symptoms)	Category (minor/ serious/ severe)	Case seen by MO I/C (Yes/No)	CRF filled (Yes/ No)
10	HSC 1	Monika	Prabhakaran	1 day	07-03-2018	BCG, Hep B, OPV	BCG037G5041 Hep B 3421A91 OPV S - 151	Abscess	Severe	Yes	Yes
10	HSC 2	Hari Prasanth	Satya Prakash	20 months	07-03-2018	DPT, Measles	DPT TA627B/14 Measles 003FS084	Fever, local pain and swelling	Minor	Yes	No
11	HSC 1	Shanti	Subramani	1.5 months	14-03-2018	Penta, OPV	TA651A/14 OPV S - 151	Seizures, febrile	Severe	Yes	Yes
11	HSC 2	Kavitha	Suresh	3.5 months	14-03-2018	Penta, OPV	TA651A/14 OPV S - 151	Mild fever	Minor	No	No
11	HSC 3	Rajesh	Sridhar	2.5 months	14-03-2018	Penta, OPV	TA651A/14 OPV S - 151	Fever (> 102*F)	Severe	Yes	Yes
12	HSC 1	Hamsaveni	Baskar	9 months	21-03-2018	Measles	003FS084	Local skin rash	Minor	Yes	No
12	HSC 2	Mayura	Madhavan	20 days	21-03-2018	BCG, OPV	BCG037G5041 OPV S - 151	Death	Serious	Yes	Yes
13	HSC 1	Preetham	Ravikumar	18 months	28-03-2018	Measles	Measles 003FS084	Fever, local pain and swelling	Minor	No	No
13	HSC 3	Baby of Kavitha	Venkatesh	1 day	28-03-2018	BCG, OPV	BCG037G5041 OPV S - 151	Localized skin redness	Minor	Yes	No

Studying the line list and answering the following questions will help the medical officer to analyse trends in reporting of AEFIs in the AEFI registers:

Whether all the serious/severe AEFI cases recorded in the AEFI register have been reported through SAFE-VAC?	Yes/No
Is there an increased trend of reporting of minor AEFI (pain, fever, swelling) with respect to a particular vaccine batch?	Yes/No
Are there specific events (e.g. abscesses) indicating unsafe administration of antigens?	Yes/No

Key Points at Sub-District Level

- Ensure availability of emergency drugs (within the expiry period) and functional medical equipment (both in the AEFI management kit at PHC and the anaphylaxis kit available with the ANM) to deal with an adverse event.
- Ensure that all necessary logistics including syrup Paracetamol, syringes, MCP card etc are available in adequate quantity at the planning unit
- Ensure the availability of anaphylaxis kit with all ANMs at session sites / sub-centres during field visits. MO should also examine and certify the contents of the anaphylaxis kit, at least once a quarter, so that drugs do not have expiry dates within the next three months and adrenaline dose chart is available in the kit.
- The line list of serious, severe and non-serious AEFI should be maintained at the Block PHC/CHC in the AEFI register.
- During the weekly review meeting the MO will refer to the AEFI register and enquire for the missed cases (minor, serious, severe) from the ANM. The MO will sign the AEFI register after all the cases of the week have been entered, and if no case is recorded in the register, he/she will mention 'No case reported' and sign.
- Ensure regular feedback is given to ANMs on previously reported cases.

5. Implement QMS for AEFIs

Implement QMS for AEFIs at the PHC and Session sites as per the quality guidelines for AEFI surveillance.

9.3.5 AEFI Committees

From the district level onwards, the AEFI surveillance activities are guided by the AEFI committees at the respective levels. The overall responsibility of the AEFI committees is to strengthen AEFI surveillance at all levels. The core actions of the committees are to -

- Ensure national policy and standards are implemented and maintained, prompt and thorough case investigation of serious/severe AEFI is done and no serious/severe AEFI cases are missed.
- Review the trend of non-serious AEFI cases being reported through HMIS/ routine immunization reporting and the status of operationalization of AEFI registers
- Undertake investigation of the AEFI cases, if indicated and monitor the performance of the AEFI surveillance system

- Causally assess the reported AEFI cases (applicable for national and state AEFI committees) as per the globally accepted classification and assessment system.
- Respond to media and community concerns to allay fears regarding vaccine safety
- Provide necessary support for strengthening AEFI surveillance through handholding and facilitating training and workshops
- Provide feedback to reporting sites and strengthen AEFI case management and closure

Please note: The AEFI committees provide technical inputs to review the factors leading to the adverse event and give suggestions to improve the system to provide safe and effective immunization. They are NOT intended to blame any health facility or an individual.

9.3.5.1 Composition of AEFI Committees

Various medical specialists, programme officers, representatives of the professional bodies are usually the members of the AEFI committees at all levels. Based on the availability of the experts at various levels (national, state and district), committee members can be sub-classified as core members and liaison members (Table 9.3).

The chairperson of the State/District AEFI committee should preferably be a paediatrician, epidemiologist or public health specialist. In addition to the chairperson, another person from the above three specialities may also be nominated as member of AEFI committee. The immunization programme manager (national/state/district) is the member-secretary.

Table 9.3: Desired Composition of AEFI Committees

Designation	National Level	State Level	District Level
Independent Members			
Paediatrician	✓	✓	✓
Public Health Specialist	✓	✓	✓
Medical Epidemiologist	✓	✓	✓
Medical Microbiologist	✓	✓	✓
Internal Medicine Specialist	✓	✓	✓
Cardiologist	✓	✓	✓
Pulmonologist/Respiratory medicine specialist	✓	✓	
Obstetrician-gynaecologist	✓	✓	✓
Pathologist	✓	✓	✓
Forensic expert	✓	✓	✓
Medical Pharmacologist	✓	✓	
Neurologist	✓	✓	
Virologist	✓		
Immunologist	✓		

Designation	National	State	District
Liaison Members			
Representative of drug authority	✓	✓	✓
Members from professional bodies like IAP, IMA	✓	✓	✓
Representatives from partner agencies like WHO/ NPSN, UNICEF (as ex-officio members; may be invited whenever required)	✓	✓	✓
Representative from IDSP		✓	✓
Cold chain officer or Vaccine and cold chain manager		✓	✓
Representative (Medical Officers) from local bodies like municipal corporations, urban local body, ESI hospital, etc.			✓
Representative from ADR monitoring centre, wherever available			✓
Representative of Quality Assurance (QA) cell at district, state level shall also be invited as special invitees		✓	✓

Apart from the above, other members could be inducted as desired by the committee at all levels or on a case-to-case basis. The preference should be given to specialists working in medical colleges to chair/be a part of the AEFI committee.

Recommended quorum i.e., the minimum number of members that must be present for the meeting to make the proceedings valid:

- District level- A minimum of five members (two independent and three liaison members) including the chairperson, paediatrician and public health specialist.
- State level- At least seven members (three independent and four liaison members) including the chairperson, paediatrician, public health specialist, forensic expert, microbiologist/ pathologist.
- National level- At least 10 members (five independent and five liaison members) including the chairperson, advisor, paediatrician, public health specialist, forensic expert, and any other.

The specific roles of concerned personnel and committees at the different levels are elaborated in sections below.

9.3.6 District level

District Immunization Officer

The DIO is responsible for ensuring that the AEFI surveillance system is functional in the district and all health workers are aware of the process of reporting AEFI. He should also ensure that the district AEFI committee meets at least once every quarter but it can meet more frequently as per the needs. It is the DIO's responsibility to ensure that all the serious/ severe AEFI cases are entered in SAFE-VAC. The DIO should also ensure that all the reported cases are thoroughly investigated, both in field and hospital and forms are complete in all

aspects including post-mortem reports, histochemical analysis, along with hospital records. DIO should also facilitate post-mortem examinations, and collection of histopathological and chemical analysis reports in case of investigation of deaths. Some of the key activities to be conducted at the district level are given in Table 9.4.

Table 9.4: Key Activities to be Conducted at the District Level

Component	Description
Functional District AEFI Committee	• There should be a functional district/corporation (or local bodies) AEFI committee with defined terms of reference and responsibilities (see **Annexure 15**). Ensure inclusion of all experts, especially drug inspector as per the mandated composition • Ensure that no AEFI case deserving to be investigated is ignored. • Conduct the investigation for all serious/severe AEFIs and update the state and national accordingly. • Ensure implementation of QMS activities for AEFI surveillance, in the district in terms of progress of internal and peer assessments of PHCs and activities at the district level.
Documentation and Data Entry	• Ensure adequate documentation of AEFI system is maintained and available at the district level. » Contact list of AEFI committee members, » Terms of reference of the AEFI committee, » Line listing of serious and severe AEFI cases investigated, » Case specific files with (CRF and CIF) and their supporting documents, » Analysis and presentations including spot maps » AEFI related communications such as letters, government orders (GOs), bulletins, state AEFI committee meeting minutes, feedback, vaccine sample test results, etc. • Review SAFE-VAC data, analyse AEFIs reported from planning units and HMIS. • Discuss AEFI surveillance as part of the monthly MO meeting and share feedback to PHCs/CHCs in the district and to the state.
Coordination with Various Stakeholders	• Coordinate with the Adverse Drug Reactions (ADR) Monitoring Centres of the Pharmacovigilance Programme of India to ensure that the ADR due to vaccines identified and reported by the Coordinator of the ADR Monitoring Centre in their own software is also reported to the CMO/DIO. Investigate the serious and severe cases as per the guidelines. • Coordinate with government/private medical colleges in the district to identify specialists to assist the District AEFI Committee in investigations e.g., neurologist, forensic medicine specialist, microbiologist, histopathologist, etc. • Build relations with and advocate reporting of AEFIs with members of district chapters of IAP and IMA • Ensure that personal contact details of the DIO are shared with appropriate staff in government, autonomous bodies and private health institutions undertaking vaccinations to ensure prompt reporting of AEFIs. • Ensure that key updates of the District AEFI Committee meetings are discussed and reviewed during the monthly meeting of District Task Force for Immunization and/or District Health Society.

Training and Capacity Building	• Ensure AEFI guidelines are disseminated and staff trained and sensitized to detect and respond to adverse events on time. • Designated AEFI surveillance nodal officer of medical colleges and large hospitals (govt and private) should conduct regular sensitization meetings with doctors and paramedical staff for reporting of AEFIs. DIOs and SMOs and state/zonal AEFI consultant may encourage and support such activities. • Ensure availability of blank Case Reporting Forms (CRF) at all health facilities in government and private sector with contact details of DIO for reporting of serious/severe AEFI cases • State should undertake training of DIOs on AEFI surveillance (reporting and investigation of serious and severe AEFI cases) at least once a year.
AEFI Response and Management	• Validate and complete all the details of the CRF. Ensure that the case details are entered in SAFE-VAC by the district data entry operator under the supervision of the DIO, and the case ID thus generated in SAFE-VAC be allotted to the case. Also, attach the scanned copy of the CRF and upload it on the SAFE-VAC portal. All these processes should be completed within 48 hours of case notification. • Ensure timely medical management of cases in district including coordination with local hospitals/laboratories from govt. sector, medical colleges and other private hospitals to deal with any referral/ testing or other procedures following AEFI. • Investigate all serious/severe AEFIs in coordination with the district AEFI committee at the earliest • Collect all relevant documents pertaining to a case immediately, to ensure they are not lost. • Complete the Case Investigation Form (CIF) as per the stipulated timeline (within 21 days from the date notified) and coordinate with the district AEFI committee to complete the documentation and submission of the details on SAFE-VAC portal. • Coordinate with laboratories undertaking sample testing and share the conclusions and results of investigation with appropriate levels
Within a district, a corporation may be considered as a separate entity for AEFI reporting and investigation. It should have its own independent AEFI committee. For AEFI surveillance, the Corporation Medical Officer (or MO in-charge of immunization) should perform activities as conducted by a DIO in a district. After investigation, the Corporation MO should send details to the state for causality assessment. DIO should also ensure regular feedback to the reporting units.	

9.3.7 State Level

Director FW / State Immunization Officer, State AEFI Consultant and State Drug Controller

State Immunization Officer may be supported by the state AEFI consultant to support for establishing better coordination between districts, state, and national levels. Some of the key activities to be conducted at the state level are given in Table 9.5.

Table 9.5: Key Activities to be Conducted at the State Level

Component	Description
Functional State AEFI Committee	• Strategic planning and management of AEFI activities including strengthening early detection and investigation of AEFI cases, follow up for completion of case records. • Ensure conduction of regular state AEFI committee meetings. For Terms of Reference of state AEFI committees, see **Annexure 16**, and the steps to conduct the state AEFI Committe meeting are given in **Annexure 17** • Review of serious/severe AEFI cases reported through AEFI surveillance programme and conduct causality assessments of these cases • Convey the results of the causality assessment done by the state to the national level through SAFE-VAC and, if required, present the results, to the national causality assessment sub-committee or directly to the national AEFI committee in their meetings. • Support and guide the districts to conduct AEFI field investigations and analysis • Oversee and monitor the implementation of Quality Management System for AEFI surveillance in the state and push for achieving state certification as early as possible. • Support in coordinating with other vaccine pharmacovigilance stakeholders to ensure adequate vaccine pharmacovigilance function. • Provide technical expertise in facilitating State and district level workshops and trainings for AEFI investigation and causality assessments. • Support the programme manager to conduct operational and implementational research for improving AEFI surveillance
Documentation and Data Entry	• Maintain AEFI related documentation such as contact list of AEFI committee members, the terms of reference of the AEFI committee, state line listing of serious and severe AEFI cases, completed reporting and investigation formats, case summaries and their supporting documents, causality assessment reports, spot maps and other AEFI related communications such as letters, Government Orders (GOs) etc. • Review SAFE-VAC data, analyse AEFIs reported through HMIS and other reporting channels in the state and share feedback with Government of India and the districts in state. Identify districts that are not reporting any AEFIs or are under reporting AEFIs. Review cases reported but not investigated by the districts. • Monitor reported AEFI data for any unusual increase in number of AEFI reported especially with a particular antigen or a batch and make recommendations for its further investigation and inform the national level. • Review status of AEFI surveillance during state and district review meetings and workshops. • Provide feedback of observations and recommendations of State AEFI committee, specimen testing results etc. to the concerned District Immunization Officer/District AEFI Committees. • Track district AEFI committee meetings and share tracking tool with SEPIO and State AEFI Committee for corrective actions • Undertake field visits to districts for monitoring AEFI activities

Component	Description
Coordination with Various Stakeholders	• The State Task Force for Immunization should discuss and review key updates from the State AEFI Committee in its monthly meeting. Ensure that the State Drug Controller is inducted as a member of the state AEFI committee and supports the state in lab coordination and other duties. • Ensure that the AEFI Committees of the Corporations are functional and support the immunization health officer of the corporation in AEFI surveillance • Ensure effective coordination is maintained with the state QA cell for planning and implementation of QMS-AEFI activities in the state, whenever initiated • Coordinate with the state chapters of the IMA, API and IAP to ensure reporting by private practitioners from districts. Ensure that the District Immunization Officers respond to information of AEFIs from the private sector adequately. • Strengthen AEFI surveillance in the state using the existing surveillance networks. • Ensure effective AEFI monitoring and supportive supervision. • Coordinate with government/private medical colleges for support in investigating AEFI cases by identifying specialist doctors. These can be forensic medicine specialists, neurologists, histopathologists, etc. • Coordinate with all stakeholders including state AEFI technical collaborating centres, drug regulators, Adverse Drug Monitoring Centres, IAP, API, IMA, partner organisations, strengthening AEFI surveillance. • Focus on municipal corporations, designated urban areas under Urban Health Mission for improving AEFI surveillance and functional urban AEFI committees • Co-ordinate with the Immunization Division/Senior Zonal AEFI Consultants/AEFI Secretariat regarding issues/challenges related to AEFI surveillance processes
Training and Capacity Building	• Assist in responding to AEFI and support the districts in investigation, when requested. • During visits to the districts and through monitoring and supportive supervision, ensure that the documentation (CRFs) of AEFIs which are not being investigated is up to date and verify that no AEFI worth investigation is ignored. • Ensure the national AEFI guidelines and reporting formats (CRF and CIF) are disseminated to the programme managers and other staff at the district and sub district level and ensure that there is a plan to train the staff at periodic intervals. • Ensure that the DIOs have an updated list of the Adverse Drug Reaction (ADR) Monitoring Centres in their districts and they are investigating serious and severe AEFI cases reported by the Centres. • Monitoring and implementation of continuous capacity building activities for District Immunization Officers (DIO), data entry operators, MOs, HWs and other frontline workers for AEFI surveillance activities.

AEFI Response and Management	• In case of crisis, organize/support special case investigations, coordinate implementation of crisis communication protocol including media management of AEFI cases • Offer appropriate technical and managerial support to district based on the event in question. • If required, form an investigating team with experts from state committee to investigate special cases (cluster cases with death and hospitalizations or case highlighted by the media etc.) • Check if similar event has occurred in other districts by reviewing line lists, coordinate with the DIOs and provide technical assistance (e.g., specimen collection and shipment, handling the media etc) if requested • Coordination with other state departments such as state drug authorities, hospitals/labs, medical colleges and other private hospitals to deal with any referral/testing or other procedures following AEFI • Ensure that the state communication plan is activated to handle any crises **POST EVENT** • In case of cluster events due to programme errors, state should issue appropriate instructions to the districts to prevent such cases from recurring. • Ensure all health care personnel are well oriented with regards to AEFI surveillance by conducting periodic training and refresher meetings. • Engage the state AEFI committee timely and regularly for final conclusion (causality assessment) of the reported serious AEFI. Ensure the completion of the CIFs and submission of all case records within the stipulated timeline as per the national guidelines. Coordinate with the district (and state) AEFI committees to complete the documentation and submission of the details to the national levels. • Conduct a quality causality assessment of each reported case at state level within 90 days of notification of an AEFI case • Ensure submission of all documents (including hospital records, post-mortem reports, etc.) for all AEFI cases on SAFE-VAC by the districts • Ensure that the state communication plan is activated to handle any crises.

The State AEFI Consultant/Routine Immunization Consultant should assist in the SEPIO in the above-mentioned activities. He will particularly coordinate the State AEFI Committee meetings and assist in liaison with a medical college as a state AEFI technical collaborating centre. He will report to the SEPIO and give feedback on the activities conducted to the SEPIO. The state AEFI committee meetings should be held at least once in every quarter. The SEPIO should ensure feedback an motivation to poorly/non-reporting districts.

9.3.8 National Level

National Programme Manager for Immunization, MOHFW

- Coordinate and lead the AEFI activities as the nodal person at the national level and review AEFI surveillance activities on periodic basis with the support of National AEFI Committee and national AEFI Secretariat.
- Review overall patterns of reports and investigations, revision of guidelines /SOPs,

capacity building at national and state level, maintenance of national database of serious and severe AEFI cases and providing feedback to the states.

- Conduct periodic evaluation of the AEFI surveillance system of the country
- Ensure meetings of the National AEFI Committee and sub-committees on a regular basis
- Coordinate with other important stakeholders in AEFI surveillance like regulatory bodies, pharmacovigilance programme of India etc.
- Assess requests from the state government to support in special case investigation of a suspected severe/serious AEFI case by sending a central team of experts.
- Share feedback to states on status of AEFI surveillance with suggestive action points for improvement on a regular basis.

National AEFI Committee

The National AEFI Committee should have sector-wide membership including paediatricians, community health experts, neurologist, cardiologist, respiratory medicine specialist, medical specialist, obstetrician-gynaecologist, immunologists, pharmacologists, microbiologist, pathologist, forensic medicine experts as well as the representatives from stakeholders such as CDL Kasauli, CDSCO and PvPI-IPC and professional bodies such as IAP, IMA, TNAI, etc. The national AEFI committee meeting should be held at least once every quarter or as and when required based on the priority of the Ministry of Health and Family Welfare. If required, Directors of Family Welfare, State EPI Officers and the chairpersons/members of respective State AEFI committees may also be invited on rotational basis as special invitees to attend the National AEFI Committee meetings.

The terms of reference of the Committee are as follows:

1. Provide technical guidance to the national AEFI surveillance programme, policy and implementation.
2. Update and review AEFI programme guidelines, SOPs and establish systems for quality data especially in context to new vaccines such as COVID-19 vaccine or other mass vaccination campaigns.
3. Support in strengthening of AEFI surveillance in states through handholding and facilitating trainings, workshops, as and when required.
4. Review the trends of AEFI reports on a regular basis and suggest policy interventions.
5. Review results of causality assessment done by experts at the national level (causality assessment sub-committee) or, if required, the results presented directly by the state AEFI committee and finalise/approve them and convey them to the MOHFW.
6. Assist the states in field investigation, whenever requested by the MOHFW or requested by the state.
7. Regularly review the AEFI surveillance in the country as well as implementation of QMS processes in states.
8. Suggest processes for greater integration of private sector in AEFI programme including reporting, investigation and response.
9. Strengthen integration with the national pharmacovigilance programme with partners including CDSCO and IPC and guide signal detection activities.

10. Advice the national AEFI programme on improved vaccine quality and testing facilities and collaboration with national / international institutions.
11. Suggest issues within AEFI surveillance which require research (operational/ implementation) and pilot studies to improve AEFI surveillance.
12. Develop a mechanism of regular feedback at all the levels based on the data and reports.

There are four sub committees of the National AEFI Committee. Each subcommittee has a Chair and is responsible for specific activities:

1. **Causality Assessment sub-committee** - conducts causality assessment in meetings organised monthly or more frequently as required at National level, review trends, and identifies signals in the context of introduction of new vaccines. It also ensures quality in causality assessment at state level by providing feedback, as and when required.
2. **Investigation sub-committee -** undertakes AEFI field investigations as and when requested by the Immunization Division, MOHFW and shares feedback in terms of action points to improve AEFI investigations.
3. **Laboratory sub-committee -** supports identification and establishment of a network of national / accredited laboratories across the country for testing vaccine and AEFI case samples, coordinate with the CDSCO, suggest ways and methods of ensuring quality laboratory tests and standards as applied on global level for AEFI case investigation.
4. **Media sub-committee -** Addresses the media at national/state level to handle communication around AEFIs and identify and establish a network of spokespersons in state and district level; develop an appropriate communications curriculum, communication aids/kits.

AEFI Secretariat and Zonal AEFI Senior Consultants

With the establishment of the state and the district AEFI committees, voluminous data is being received at the national level. It is essential to collate, analyse, interpret and respond to the same to arrive at a logical conclusion. As per the recommendations of National AEFI committee an AEFI secretariat has been established to strengthen AEFI reporting in the Ministry of Health and Family Welfare in 2012. It is hosted at the Immunization Technical Support Unit (ITSU) set up by the MoHFW, Government of India. The AEFI Secretariat works closely with the Immunization Division, MoHFW and the National AEFI Committee to support some of the core activities such as:

- Coordinate with Immunization Division, NRA, CDSCO, CBHI, IEC Division, and NCDC, IDSP, WHO - NPSN or other partner agencies for strengthening AEFI surveillance activities at the national and state level.
- Liaise with State/ District AEFI committees and other vaccine safety stakeholders including DCGI and PvPI to enhance vaccine safety activities in the country.
- Support in regular conduct of National AEFI committee meetings (quarterly basis) and causality assessment meetings (monthly basis).

- Support the states and state AEFI committee to ensure continuous monitoring of AEFI surveillance activities such as follow-up on timeliness and completeness of data reporting in surveillance, response and follow-up of serious AEFIs.
- Provide technical assistance to states/UTs on programme monitoring and capacity building, especially for case investigation and causality assessment process.
- Facilitate central team visits to states and districts to assist in case investigations whenever needed
- Coordinate with Causality assessment sub-committee and AEFI Technical Collaborating Centre for periodic review of causality assessments conducted by states
- Facilitate activities of National AEFI committee (including administration & logistic support) and other National, State and District level workshops and trainings.
- Support in implementation of QMS-AEFI (NQAS for AEFI surveillance) to strengthen AEFI processes
- Coordinate activities with ADR monitoring centre under PvPI at state and district level
- Review AEFI database for vaccine safety signal detection

Zonal AEFI senior consultants at National AEFI secretariat are representatives of Immunization Division, MoHFW and collaborate with allocated states to strengthen AEFI surveillance activities. They support the states by:

- Providing regular feedback to states /districts on the quality of case investigation reports and records submitted for the reported AEFI cases and performance of AEFI surveillance programme.
- Follow-up with districts for pending documents, screening cases for completion and ensure they are causally assessed at national level
- Undertake field visits to states and districts for monitoring AEFI activities, coordinating special investigation of severe/serious AEFIs of special interest and provide feedback to the Immunization Division
- Providing support in identifying and coordinating with AEFI technical collaborating centres in states.
- Advocating and coordinating with professional associations (IAP, IMA, IAPSM, etc.) for participation of private sector in AEFI surveillance programme.
- Facilitating roll out of SAFE-VAC and QMS activities
- Facilitating capacity building activities for state AEFI committees (especially in causality assessment) and district immunization officers.
- Coordinating with proposed pharmacovigilance officers/associates at state and district levels and jointly review immunisation safety data at states

9.4 Technical Collaborating Centres

The AEFI surveillance programme requires high quality clinical inputs for case investigations, diagnosis of events, recognition of individual risk factors, laboratory support, management of adverse events, etc. Such expertise in available in the medical colleges in all states. The national AEFI committee recommended that a medical college of national prominence may be identified to provide this expertise to the national AEFI secretariat. A medical college in each state may also be identified to provide similar expertise to the state immunization officer.

9.4.1 National AEFI Technical Collaborating Centre (LHMC)

A National AEFI Technical Collaborating Centre (NATCC) was set up in the Department of Paediatrics, Lady Harding Medical College, New Delhi. Currently, this technical collaborating centre provides technical oversight to the AEFI surveillance programme and clinical expertise for the causality assessment processes. It also supports in all capacity-building processes, AEFI case investigations and other activities as required. Some of the key activities being performed by the NATCC are:

1. Review the AEFI surveillance database to identify trends in reported AEFI
2. Ascertain the causality for the reported serious/severe AEFI cases
3. Support in capacity building activities
4. Provide technical support to national level and states on an immediate (crisis) and regular basis
5. Identify potential research areas for improving the quality of the AEFI surveillance system.

9.4.2 State AEFI Technical Collaborating Centre

Each state may identify a prominent medical college as a Technical Collaborating Centre for AEFI surveillance with an aim to strengthen the state capacity for technical and clinical support to office of the state EPI officer and state AEFI committee. This partnership would help strengthen the skills related with AEFI programme, including causality assessment of reported AEFI cases, field investigation of serious AEFIs, integrating drug and vaccine pharmacovigilance, quality assurance of AEFI reports, etc. The objectives and roles and responsibilities are given below:

Objectives:

1. Monitoring AEFI processes, capacity-building activities and providing feedback to AEFI secretariat/states
2. Supporting quality causality assessment and investigation of adverse events.

Roles and Responsibilities:

1. The AEFI Technical Collaborating Centre would provide expertise and a pool of resource persons for carrying out capacity building, AEFI investigation and causality assessment.
2. The Technical Collaborating Centre will serve as venue for the periodic review meetings and workshops related to AEFI.

Other possible roles:

1. Support in coordinating with other vaccine pharmacovigilance stakeholders to ensure adequate vaccine pharmacovigilance function.
2. Review AEFI database for use of data to improve AEFI surveillance in districts
3. Encourage research related to vaccine safety in the state

The network of such regional collaborating centers thus created shall enable sustainability of the AEFI programme by institutionalizing the linkages between academia and public health

programs. The state AEFI technical collaborating centres could be located in any government medical college preferably at state headquarters. The department managing the centre can be the department of paediatrics or the department of community medicine or any other department showing interest/enthusiasm. The funding could be from the state PIP and a simple MOU can be signed by the health department with the medical college.

9.5 National and State Regulatory Authority

Regulatory authorities at the national and state level play a major role in ensuring quality and safety of vaccines. The DCGI heads the national regulatory body. CDSCO is the national regulatory authority in India responsible for approving marketing authorization and ensuring post-market surveillance of vaccines. The central laboratories Central Drugs Laboratory, Kasauli and Central Drugs Laboratory Kolkata are laboratories under the aegis of CDSCO and contribute to the testing and batch release of vaccines and syringes. Indian Pharmacopeia Commission hosts the national pharmacovigilance programme of India with focus on monitoring safety of medicines and medical devices. AEFI is a vital functional component of the NRA (National Regulatory Authority). India plays a global role in supply of vaccines and exports vaccines to more than 200 countries globally, including developing countries through WHO Prerqualification Programme for Vaccines. The state drug controller heads the state regulatory authority. Please refer to Chapter 13 for more details.

9.6 Pharmacovigilance and Immunization Partners

9.6.1 Role of Immunization Partners at District, State and National Level

Partners such as WHO, UNICEF and UNDP can support the District Immunization Officer in strengthening AEFI surveillance activities by:

(a) Capacity building of health workers for AEFI surveillance
(b) Monitoring of RI sessions for observing ANM injection practices
(c) Supporting case investigation of serious/severe AEFI cases
(d) Sharing the analysis of AEFI surveillance data during state/district task force meetings on immunization
(e) Supporting the state/district in ensuring the implementation of SAFE-VAC and other AEFI related software across all states and districts

9.6.2 Role of Pharmacovigilance Partners at District, State and National Level

(a) Reporting and cross-notification of AEFIs
    (i) ADR Monitoring Centres can report vaccine adverse events to the DIO/state/national level through Case Notification Form (CNF) and email and follow it up with a telephone call.
    (i) Other ways of reporting vaccine adverse events are through the mobile app (ADR PvPI) or the toll-free number 1800 180 3024.
(b) Sharing updates on vaccine safety through mechanisms such as Periodic Safety Update Reports (PSURs)
(c) Sharing of information on signal recommendations

9.7 Quality Assurance of the AEFI Surveillance System

The Quality Improvement Division of NHSRC, New Delhi supported the development of the National Quality Assurance Standards for AEFI Surveillance in 2016. Guideline of NQAS for AEFI Surveillance contains benchmarks, checklists and scoring systems for AEFI surveillance activities. Standard Operating Procedures (SOP) have been developed and QMS has been implemented followed by quality certification for the national level AEFI surveillance processes. The benefits accrued due to implementation of quality management system in a surveillance programme will be similar to that in a health care facility setting which focuses on improving quality of care for patients. Quality management system in AEFI surveillance is expected to lead to standardization of processes, clarity in responsibility and accountability, greater efficiency and improved quality of surveillance. Different areas of concern have been identified at various levels – immunization site, district, state and national level for which periodic internal, peer and external assessment and certification needs to be undertaken using standardized checklists and methods. Please refer to Chapter 12 and the National Quality Assurance Standards for AEFI Surveillance Program available at https://main.mohfw.gov.in/sites/default/files/National%20Quality%20Assurance%20Standard%20AEFI%20on%2022-11-16%20B.pdf for further details.

9.8 Signal Management of Vaccines

Based on the signal management framework for vaccines developed for the country, a signal review panel (SRP) was constituted at the national level. It is an independent body formed to assess information on potential signals of importance for public health, drug regulation, and science from the databases for adverse events following all vaccines. The SRP meets every two months or earlier, if required and reports its findings and recommendations to the National AEFI Committee and the MOHFW. The AEFI Secretariat analyses the data and presents it to the SRP and follows up on the recommendations of the SRP. For more details regarding signal management processes, refer to Chapter 10.

9.9 Liaison with the District Administration and Police

Police officers and the district administration work in partnership with the public. They are citizen-focused, responding to the needs of individuals and communities.

Serious AEFIs resulting in death/cluster of events may also be investigated in parallel by the police and the district administration to rule out any criminal intent or negligence in the event, in some cases. In some cases, the police would also be participating in the process of investigation, conducting autopsies, collecting specimens and testing the same in specialized laboratories.

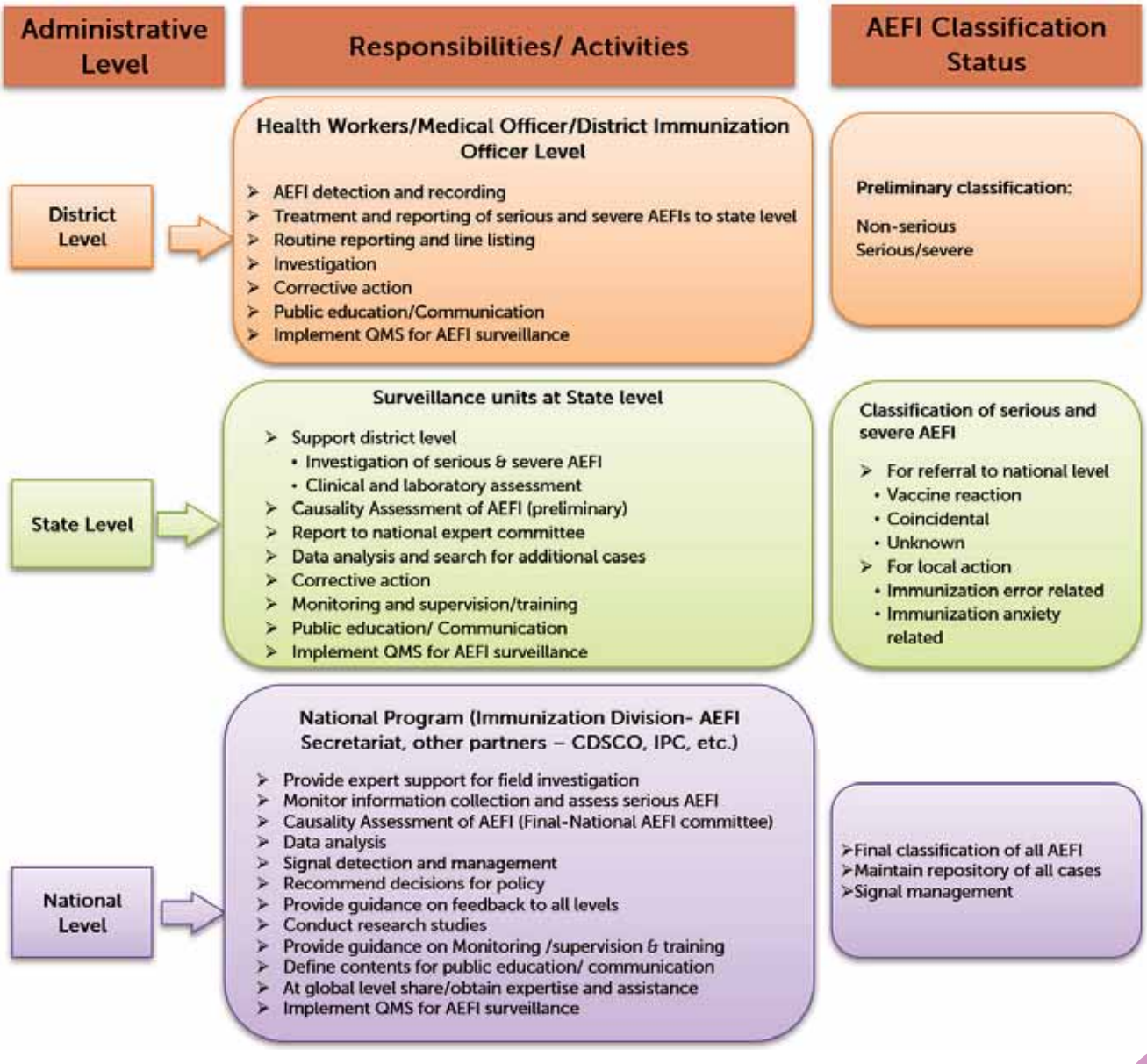
It is important to remember that the goal of the district AEFI committee, the district administration and the police are identical i.e., to arrive at a conclusion on the cause of the

adverse event that resulted in death. ***If required, the AEFI committees may invite the police and district administration to participate in the AEFI investigation planning meetings, visit the sites together for investigation, and jointly collect specimens as far as possible, wherever police are involved in AEFI case.***

However, it is important to consider that the protocols for different agencies investigating the AEFI will be different and therefore the investigating officers need to handle the situation tactfully ensuring coordination between partners and stakeholders. They also need to be updated on the findings as the investigation proceeds logically to its conclusion.

There are multiple stakeholders and partners working together at different levels to achieve common objectives at that level. Figure 9.2 shows a schematic diagram showing the broad responsibilities and activities related to AEFI surveillance at different levels of programme implementation.

Figure 9.2: AEFI Surveillance - Responsibilities and Activities



9.10 Performance of the AEFI Surveillance System

The AEFI surveillance system needs to be regularly monitored at all levels to ensure that the system is sensitive enough to identify and respond to AEFI rapidly. Some of the recommended indicators to monitor the performance of the AEFI surveillance programme at different levels are discussed below.

9.10.1 Indicators for AEFI Surveillance

The indicators for the AEFI surveillance for sub- district, district, state and national levels for activities such as reporting, investigation, causality assessment and QMS-AEFIs are listed in Table 9.6.

Table 9.6: Indicators for AEFI Surveillance

A	At Sub-District Level - to be Assessed by MOI/C		
Reporting Indicator		**Formula**	**Benchmark**
1.	Proportion of serious or severe AEFI cases reported to the district through CRF	No. of serious or severe AEFI cases reported to the district through CRF/Total no. of serious or severe AEFI cases listed in the AEFI register *100	>90% (Data to be assessed on quarterly basis)
2.	Proportion of sub-centre immunization sites scoring at least 70% in internal assessment (QMS indicator for PHC/ Immunization Site)	No. of sub-centre immunization sites scoring at least 70% in internal assessment/Total number of subcentre immunization sites in the PHC area *100	50% of the sub-centre score at least 70% in internal assessment. (Data to be assessed on quarterly basis)
B	**At District Level - to be Assessed by DIO**		
Reporting Indicator		**Formula**	**Benchmark**
1.	District AEFI reporting rate	No. of serious or severe AEFI cases reported through CRF on SAFE-VAC in a year/No. of surviving infants in a district in a year * 10,000	It is expected that at least 1 serious/ severe AEFI case per year per 10,000 surviving infants should be reported (Data to be assessed on quarterly basis)
2.	AEFI report completion rate	No. of serious or severe AEFI cases with both CRF and CIF uploaded on SAFE-VAC/No. of serious or severe AEFI cases initiated on SAFE-VAC *100	>80% (Half yearly data to be assessed after completion of next quarter i.e., for the cases reported in the Jan-Jun period, assessment can be done in Sept)
3.	Timeliness of CRF reporting	No. of serious or severe AEFI cases with its CRF uploaded on SAFE-VAC within 48 hours of notification/Total no. of serious or severe AEFI cases reported on SAFE-VAC * 100	>90% (Data to be assessed on quarterly basis)

Investigation Indicator			
1	Timeliness for CIF completion	No. of serious or severe AEFI cases with CIF uploaded on SAFE-VAC within 21 days of notification/Total no. of serious/severe AEFI cases reported on SAFE-VAC * 100	> 80% (Data to be assessed on quarterly basis)
Programmatic Indicator			
1.	Proportion of District AEFI Committee (DAC) meetings held	No. of DAC meetings held in a year/Total no. of DAC meetings expected to be held in a year*100	100% (At least 1 DAC meeting should be held in each quarter)
2.	Proportion of minutes of DAC meetings shared with the state (Use district AEFI committee meeting tracking tool as evidence for this indicator)	No. of minutes of DAC meetings shared with state/ Total no. of DAC meetings held in a year*100	100% (Minutes of every DAC meeting should be shared by the district with the state within a fortnight of completion of the meeting)
3.	Proportion of PHCs in the district obtaining at least 70% score in internal assessment (in addition to district level also scoring at least 70% score in internal assessment) (QMS indicator for district)	No. of PHCs scoring at least 70% in internal assessment/ Total number of PHCs in the district*100	50% of district PHCs score at least 70% in internal assessment. (Data to be assessed on quarterly basis)
C	**At state level - to be assessed by SEPIO**		
Reporting Indicator		**Formula**	**Benchmark**
1.	State AEFI reporting rate	No. of serious or severe AEFI cases reported through CRF on SAFE-VAC in a year/No. of surviving infants in a state in a year * 10,000	It is expected that at least >1 serious or severe AEFI cases should be reported per 10,000 surviving infants in a year (Data to be assessed on quarterly basis)
2.	Proportion of reporting districts in the state/UT	No. of districts reporting any serious or severe AEFI case in a year/Total no. of districts in the state or UT *100	>80% (Data to be assessed on quarterly basis)

3.	Timeliness of CRF reporting	No. of serious or severe AEFI cases with its CRF uploaded on SAFE-VAC within 48 hours of notification/Total no. of serious or severe AEFI cases reported on SAFE-VAC * 100	>90% (Data can be assessed on quarterly basis)
Investigation Indicator			
1.	Timeliness of CIF reporting	No. of serious or severe AEFI cases with CIF uploaded on SAFE-VAC within 21 days of notification/Total no. of serious/severe AEFI cases reported on SAFE-VAC * 100	> 80% (Data can be assessed on quarterly basis)
Causality Assessment Indicators			
1.	State causality assessment rate	No. of serious or severe AEFI cases reviewed and classified by the state AEFI committee and uploaded on SAFE-VAC/ No. of serious or severe AEFI cases reported in the state*100	> 80% (Data can be assessed on half yearly basis)
2.	Timeliness for causality assessment	No. of serious or severe AEFI cases reviewed and classified by the state AEFI committee and uploaded on SAFE-VAC within 100 days of case notification/No. of serious or severe AEFI cases causally assessed by the state * 100	> 80% (Data can be assessed on half yearly basis)
3.	Proportion of ineligible case	Total no. of serious or severe AEFI cases categorized as ineligible by the experts of the state AEFI committee/ Total no. of cases reviewed and classified by the committee*100	<20%
Programmatic Indicators			
1.	Proportion of State AEFI Committee (SAC) meetings held	No. of SAC meetings held in a year/Total no. of SAC meetings expected to be held in a year*100	100% (At least 1 SAC meeting should be held in each quarter)
2.	Proportion of minutes of SAC meetings shared with the national level	No. of minutes of SAC meetings shared with national level/Total no. of SAC meetings held in a year*100	100% (Minutes of every SAC meeting should be shared by the state with the national within a fortnight of completion of the meeting)

3.	Proportion of districts achieving at least 70% scores in peer assessment (and state level activities achieve at least 70% scores) - QMS indicator at state level	No. of districts scoring at least 70% score in internal assessment/Total number of districts in the state * 100	50% of the districts in the state achieve 70% score in peer assessment for state to be eligible for peer/external assessment. (assessed on yearly basis)
D	**At national level – to be assessed by Immunization Division/AEFI Secretariat**		
Reporting Indicator		**Formula**	**Benchmark**
1.	National AEFI reporting rate	No. of serious or severe AEFI cases reported through CRF on SAFE-VAC in a year/No. of surviving infants in the country in a year * 10,000	It is expected that at least 1 serious or severe AEFI cases should be reported per 10,000 surviving infants in a year
2.	Proportion of reporting districts	No. of districts reporting at least one serious or severe AEFI case in a year/Total no. of districts in the country *100	>80% (Data to be assessed on quarterly basis)
3.	Timeliness of CRF reporting	No. of serious/severe AEFI cases with its CRF uploaded on SAFE-VAC within 48 hours of notification/Total no. of serious/severe AEFI cases reported on SAFE-VAC * 100	>90% (Data can be assessed on quarterly basis)
Investigation Indicator			
1.	Proportion of serious / severe AEFI cases with CIF uploaded in SAFE-VAC for the states and districts	No. of serious/severe AEFI cases with CIF uploaded on SAFE-VAC/Total no. of serious/severe AEFI cases reported on SAFE-VAC * 100	> 80% (Data can be assessed on quarterly basis)
2.	Proportion of serious/severe AEFI cases with Case Investigation Form (CIF) uploaded on SAFE-VAC within recommended time i.e., 21 days of notification	No. of serious/severe AEFI cases with CIF uploaded on SAFE-VAC within 21 days of notification/Total no. of serious/severe AEFI cases reported on SAFE-VAC * 100	> 80% (Data can be assessed on quarterly basis)

Causality Assessment Indicators			
1.	Proportion of ineligible case	Total no. of serious/severe AEFI cases categorized as ineligible by the experts of the national causality assessment sub-committee or national AEFI committee/Total no. of serious/severe cases reported*100	<20%
2.	National causality assessment rate	Total no. of serious/severe AEFI cases causally assessed and approved at national level/Total no. of serious/ severe AEFI cases reported *100	>80%
Programmatic Indicators			
1.	Proportion of national AEFI committee meetings held in a year	No. of national AEFI committee meetings held in a year/4	Should be = or > 1 (at least one national AEFI committee meeting should be held every quarter)

9.10.2 Ranking of States - Key AEFI Performance Indicators

Immunization Division, MoHFW has initiated a system of ranking states based on their performance for AEFI surveillance activities in each quarter. Each state is expected to achieve a certain benchmark in three core areas of AEFI surveillance-reporting, case investigation and state level processes. Each core area is further sub-divided into indicators and each of these indicators have been assigned a weighted average. The compilation of all these scores leads to the overall score of the state. The ranking of states is shared once a quarter with all states with suggestions for improvements. The idea is to bring in a spirit of competition to improve AEFI surveillance.

Other information shared with the states on regular basis to improve/strengthen AEFI surveillance are as follows:

- Mismatch between deaths reported as AEFIs through CRF on SAFE-VAC and in HMIS.
- Results of causality assessment approved by the national AEFI committee
- AEFI dashboards as part of immunization dashboards

Summary

- The goal of AEFI surveillance is to ensure that vaccines used in the country are safe and public confidence in vaccine is sustained.
- An effective AEFI surveillance helps to promptly detect, report and respond to AEFI, identify programmatic errors and implement corrective measures, document the rates of AEFI for a specific vaccine, specific lot or brand in a specific region/population, identify signals of unexpected adverse events.
- Some of the key activities of AEFI surveillance include formulation of SOPs, building capacity of various stakeholders at national/state/district level, ensuring rapid notification and investigation of an AEFI, conducting causality assessment for reported AEFI cases at state level and national levels and regular feedback to state/district level programme managers
- There are many stakeholders involved in AEFI surveillance at various levels and all have specific roles and clear terms of reference.
- Coordination amongst stakeholders is key to a strong AEFI surveillance system.
- Specific AEFI surveillance indicators related to reporting, investigations, causality assessments and conduction of committee meetings exist for different levels to measure performance and improve surveillance.

10 Signal Detection and Management for Vaccines

10.1 Safety Signals

A vaccine safety signal is information that indicates a potential link between a vaccine and a previously unknown or incompletely documented event. Council for International Organizations of Medical Sciences 2010 defines a signal as "Information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a vaccine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."

A structured approach for spontaneous reporting of AEFI is a basic element of vaccine safety monitoring. The evaluation of safety signals is part of vaccine vigilance and is essential to ensure that regulatory authorities and immunization programmes have the most up-to-date information on benefits and risks. The benefit-risk balance of many vaccines is dynamic and may change over time, or may appear to change over time, and this may impact pharmacovigilance activities.

10.2 Signal Management Process

The rapid detection of vaccine safety signals of global importance is complemented by a scientifically sound assessment of the signals through the signal management process performed to determine whether there are new risks associated with a vaccine or whether known risks have changed and includes any related recommendations, decisions, communications and tracking.

The signal management process includes the following steps: signal detection, validation, confirmation, analysis, prioritization, evaluation, recommended actions, tracking of follow-up activities, communication, and risk minimization (Figure 10.1).

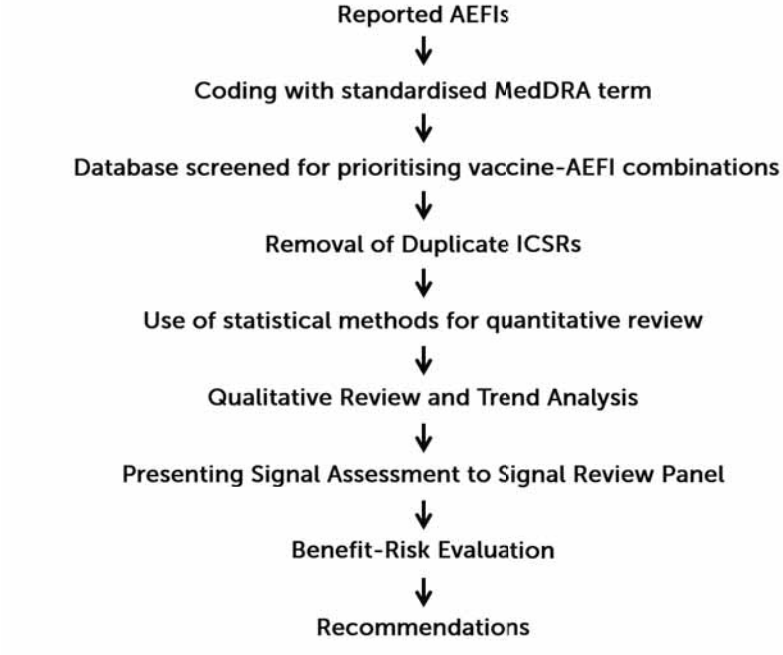
Figure 10.1: Steps of Signal Management

Signal Detection is identifying signals using data from any source. *Signal Validation* is the evaluation of the data supporting the identified signal to verify if the documentation is sufficient to confirm the existence of a cause-effect relationship. *Signal Analysis and Prioritization* is the identification of signals that require immediate management. These include signals that present significant risks to public health or that influence the benefit-risk balance of a drug. *Signal Assessment* is the evaluation of the signal in order to detect any new risks, or changes thereof, with a causal association related to the drug and to determine any necessary regulatory actions. *Recommendations* are suggestions to take further action, if required.

Statistical measures of disproportionality are used for reporting of vaccine-event pairs and are referred to as Signals of Disproportionate Reporting (SDR). At the AEFI Secretariat at ITSU, the AEFI database is screened regularly for SDRs. SDRs are considered present when the measures of disproportionality or the number of individual cases exceed certain thresholds based on the method of disproportionality used. Proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN) and reporting odds ratios (ROR) are applied on the Medical Dictionary for Regulatory Activities (MedDRA)-coded AEFI database to detect and validate potential signals. The statistical methods measure a reporting relationship between an antigen and an adverse event on the basis of a relative increase in the proportion of individual cases related to an adverse event i.e. SDR.

The signals identified statistically through disproportionate reporting are systematically evaluated and undergo detailed qualitative assessment as part of the evaluation process. Signal assessment refers to the scientific evaluation of all the available evidence, including additional data from Marketing Authorization Holders (MAHs), where applicable. Important sources for signal assessment are Individual Case Safety Reports (ICSRs), other AEFI databases, pre-clinical and clinical trials and published literature. The steps followed at AEFI Secretariat are listed in Figure 10.2.

Figure 10.2: Signal Management Process at AEFI Secretariat



The recommendation may include any or a combination of the following:

1. No need for further evaluation or action at this point in time, other than routine pharmacovigilance
2. Need for additional information:
   - manufacturer should submit additional data regarding the signal available with it
   - manufacturer should address the signal in the appropriate ad-hoc regulatory documents
   - other scientific committees or expert groups should be consulted
   - manufacturer(s) should conduct a post-authorisation safety study and submit its final results
3. Need for regulatory action:
   - the product information and/or risk management plan (RMP) should be updated with specific recommended changes.
   - Implement additional risk minimization measures such as the preparation of educational materials, or the dissemination of Direct Healthcare Professional Communication etc.

Considerations of risk-benefit with regard to the impact on patients' or public health is kept in mind throughout the decision-making process.

Assessing a causal relationship between the vaccine and the signal requires appropriately designed epidemiological studies (case-control, cohort, self-controlled case series, case crossover, etc.). The design of these studies may vary widely depending on the signal, the vaccine, risk intervals and the type of surveillance. Laboratory studies (pathological, microbiological or immunological) may also be required to provide evidence of the causal link.

10.3 Signal Management Process in India

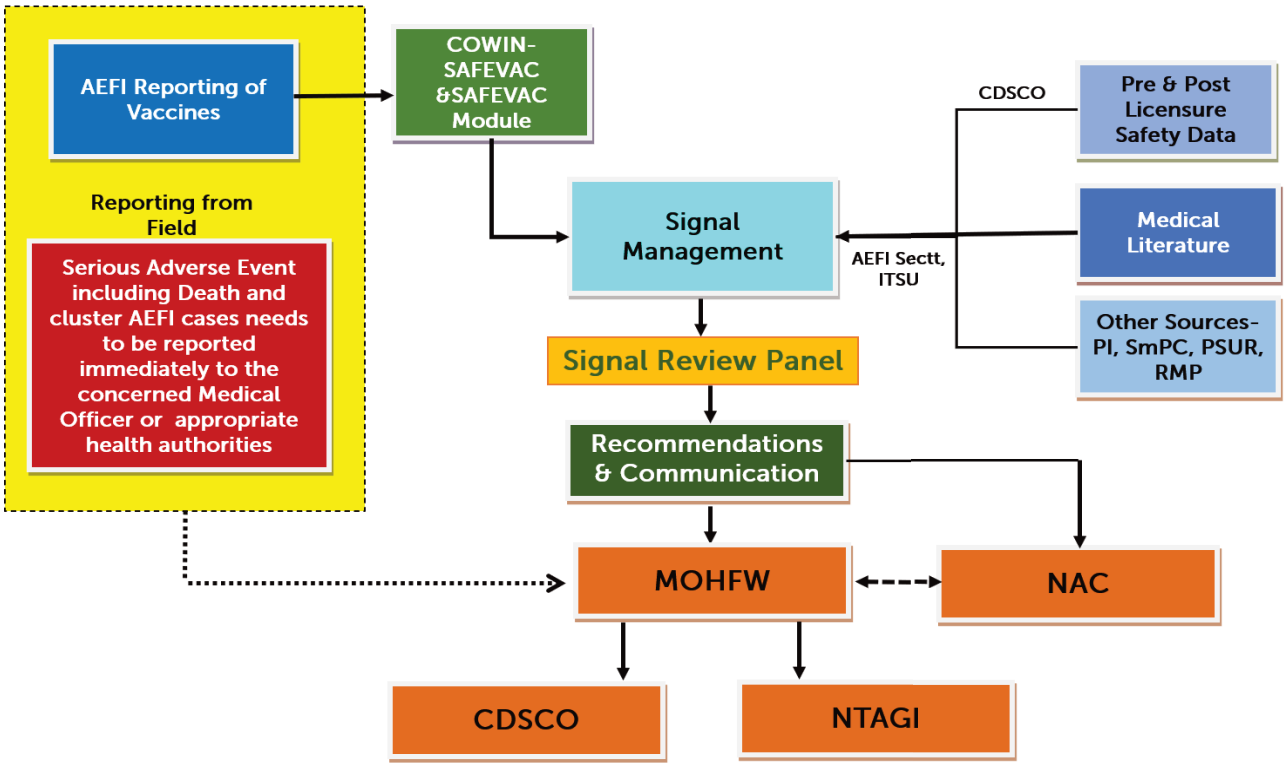
A dedicated structured system for signal management for vaccines has been set up in India. A stepwise process which included training and capacity building activities supported by international experts and organizations working in this area was initiated. A working group of experts took the lead in the development of a Signal Management Framework for Adverse Event Following Immunization (AEFI) as part of the overall vaccine safety surveillance system for India.

Based on the signal management framework for vaccines developed for the country, a signal review panel (SRP) was constituted at the national level. It is an independent body formed to assess information on potential signals of importance for public health, drug regulation, and science from the databases for adverse events following all vaccines. It consists of experienced professionals in the field of clinical pharmacology, medicine, infectious diseases, paediatrics, neurology, cardiology, and regulatory authority members, among others. A few members of the national AEFI committee are part of the Signal Review Panel. The SRP meets every two months or earlier, if required and reports its findings and recommendations to the National

AEFI Committee and the MOHFW. The AEFI Secretariat analyses the data and presents it to the SRP and follows up on the recommendations of the SRP.

The regulatory recommendations from the signal review panel are shared with CDSCO. The CDSCO sends the recommendations for further action with Marketing Authorization Holders (MAHs) such as inclusion of recommended adverse events in the Summary of Product Characteristics for the said vaccine, among others. (Figure 10.3).

Figure 10.3: Signal Management Process for Vaccines in India



MOHFW: Ministry of Health and Family Welfare (Immunization Division); AEFI Sectt, ITSU: Adverse Events Following Immunization Secretariat, Immunization Technical Support Unit, Immunization Division, MOHFW; NAC: National AEFI Committee; CDSCO: Central Drugs Standard Control Organisation (DCGI office); NTAGI: National Technical Advisory Group on Immunization; PI: Prescribing Information; SmPC: Summary of Product Characteristics; RMP: Risk Management Plan; PSUR: Periodic Safety Update Report

On priority, the Signal Review Panel has completed the assessment of the COVID-19 AEFI database and is conducting risk-benefit assessment of other vaccines which are routinely administered.

Summary

- Signal management is a national-level process which includes the following steps: signal detection, validation, confirmation, analysis, prioritization, evaluation, recommended actions, tracking of follow-up activities, communication, and risk minimization.
- The objective of the signal management system is to continuously conduct risk-benefit assessment of vaccines and provide recommendations to vaccine vigilance stakeholders including further risk communications and risk minimization efforts.
- The AEFI surveillance database is analysed for potential signals (vaccine -event pairs), which are then systematically assessed using quantitative and qualitative methods for risk and benefit. This is a continuous process.
- A signal review panel consisting of independent experts reviews the data related to potential vaccine safety signals and recommends regulatory actions which are shared with the national AEFI committee and the MOHFW for further communication to vaccine vigilance stakeholders such manufacturers.
- Considerations of risk-benefit with regard to the impact on patients' or public health are kept in mind throughout the decision-making process
- It is operationalised by the AEFI Secretariat, Ministry of Health & Family Welfare, Government of India as part of the vaccine safety surveillance system for India.

11 Vaccine Risk Communication

A routine immunization communication plan should address both short-term crisis situations (for example, when an AEFI occurs) and long-term support that the immunization programme requires. The crisis communication plan needs to be an integral part of an overall communication plan for routine immunization.

11.1 Communication for Vaccine Safety

Communication is an important and integral component of any public health programme. Cooperation from the community is crucial to the success of such programmes. The community will actively take part in a public health programme if the benefits of the programme and the need for interventions are properly communicated to the stakeholders. An example of this is the acceptance of the cost and inconvenience of using bed nets even in hot and humid conditions by people in malaria-endemic regions, as they are aware of the risks and consequences of not using bed nets.

Vaccines are given to healthy individuals mostly infants and children to protect them against diseases that they may suffer from in the future. Hence the threshold for acceptance of the risk of any side effects following vaccinations is much lower. The vaccines may be repeated as per the dose schedules and mostly are in the form of injections which can be painful as well as carry the risk of adverse events (actual, perceived or coincidental). With diseases under control due to higher immunization coverage, the acceptance of vaccination by caregivers must come as a natural choice, but it does not happen many a time. The gap can be explained due to ignorance, misinformation and lack of or ineffective communication and advocacy. Effective behaviour change communication is the key to the success of public health campaigns. Communication needs to be undertaken both as a proactive strategy to inform, educate and communicate with various target groups in the community and also as a reactive strategy in case of adverse events following immunization (AEFIs). If people are well informed, it is much easier to handle AEFI situations. Media has to be taken on board as a partner and not be seen as an adversary or only a tool of information dissemination.

Effective communication around vaccine safety, including management of public reactions, requires serious investment of resources and efforts into strategic communication for immunization. Strategic communication is an evidence-based, result-oriented process, undertaken in consultation with the participant group(s).

11.1.1 Media and Public Health

Public health may not necessarily be a priority coverage option for news media in general, but adverse events in public health do often occupy prime space and time in various news like print, electronic, and social media. The social media platforms have changed the way people, in general, consume news and react to it. It is here that people in charge of communication in the public health arena need to understand the importance of the changing contours of this phenomenon and be proactive in their approach.

Before we understand the crisis in the context of immunization and the need for planning for crisis management, it is important to know about the media ecosystem in the country to understand the media bandwidth, its sociology and its role in the dissemination of information and the consequent impact on influencing public opinion on issues of public interest.

Media in India

India has a mind-boggling media bandwidth, which is unparalleled in the world. The governments, both at the center and states have large public relations/information setups that engage with the news media constantly, for two reasons. One is to reach out to people and various constituencies through mass media on issues of public welfare including public health as it has a large reach and two, for damage control on media reporting which may not always be factual and may result in the spread of misinformation.

Print Media

From a mere 200 publications at the time of independence in 1947, today there are more than 1.46 lakh publications in India, out of which almost 17000 are newspapers, the largest number in any country. As per the RNI (Registrar of Newspapers of India), the total circulation of publications increased from 38,64,82,373 copies per publishing day in 2020-21 to 39,17,12,282 copies per publishing day in 2021-22.

News Channels

There are over a thousand television channels, out of which over 400 are news channels, which broadcasts news 24x7 in various languages including English and Hindi. While the television viewership across India is over 90%, the news channels do not command much viewership (less than two digits). In times of crisis, however, one has seen a huge surge in viewership. For instance, during the COVID-19 pandemic, the viewership overall surged from 7% to 21%.

Online Media

There has been exponential growth in online media in the last few years. Most of the newspapers and news channels can also now be accessed online. There were 833 million Internet users as of July 2022, comprising 59% of the population (Internetworldstats.com). India has the second largest number of internet users in the world after China.

Radio

Radio in India has a reach of almost 99% population. There are many FM radio stations for entertainment. The news however can be broadcast only by the All India Radio in the radio genre. The listenership of radio per se has gone tremendously down with a large surge in the ownership of mobile phones.

News media is referred as the 'Fourth Estate' in a democracy and has the power to influence public opinion. An average person makes sense of the world around her/him based on media stimuli. News media generally functions on the basic premise that it is the 'bad news' that must get precedence over the 'good news'. The argument often posited by media for this argument is its 'watchdog' function, which empowers it to question on behalf of the public those in power, especially on critical issues.

Sociology of News Media

The news media in India is owned and controlled by various interests, corporate, political, and individual among others. Except for the All India Radio (AIR) and Doordarshan News, all the other news channels are in the private sector. The print and online media is entirely in the private sector. Both newspapers and television channels are in most cases owned by large corporates and international funding organizations/ agencies. With the kind of access and impact of news media, it will be easier to understand why media has to be taken seriously and how to manage relations and sensitize it on immunization, both in normal and critical times.

11.2 Regular Routine Immunization Communication

Communication activities for routine immunization during regular days should follow a plan. This plan is usually prepared once a year with an approved budget, implemented throughout the year and revolves around the regular and pre-planned routine immunization activities. It is also the opportunity to prepare communication plans for crisis situations in routine immunization. This is a resource-intensive activity as the state and district have to plan and prepare for all types of potential crisis situations. It requires a good understanding of the crisis situation both at the community /grassroots level, as well as knowledge and skills for interacting with the media to ensure it does not explode at a higher level.

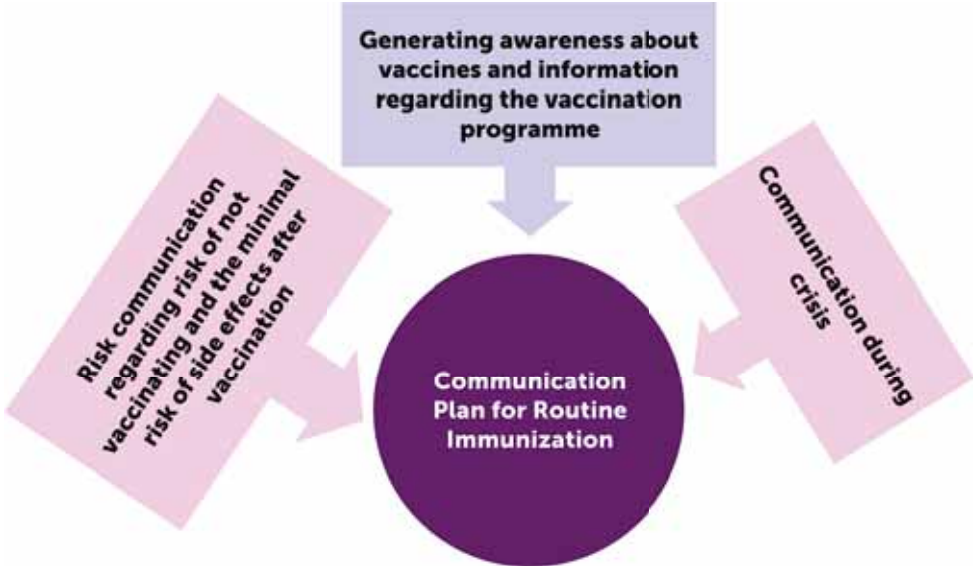
11.2.1 Communication Plan for Routine Immunization

An ideal routine immunization communication plan should cater to the following:

1. Generating community awareness about the importance of immunization, how it proactively protects against diseases; where and when vaccines are administered free of cost and at what ages.
2. Address the barriers to demand generation which includes hesitancy to return for subsequent doses because of the fear or discomfort following vaccinations (vaccine risk communication).
3. Engage with community and media whenever there is a crisis affecting trust in vaccines.

In addition to the awareness generation and information activities, the district communication plan should also address issues of vaccine safety and include a plan for communication during crisis situations such as AEFIs (Figure 11.1). It is important that the plan should also include components of identifying hesitant groups or groups showing reluctance to get vaccinated and address their concerns in a systematic and focused manner. Addressing vaccine safety issues and preparing for crisis situations in RI should be done when there is no crisis.

Figure 11.1: Routine Immunization Communication Plan Components



An ideal programme will have a media mix comprising IPC (interpersonal communication) channels for reaching out to communities in an informal setup, mass media (newspapers, TV channels, cinema theatres viewing, social media) and outdoor media including, banners, posters, billboards to serve as a reminder media and advocacy literature for creating an overall communication ecosystem on RI. In short, the choice of media will depend on need and particular challenges, threats and potential impact on vaccine confidence (Table 11.1).

Table 11.1: Intensity of Objective based Communication Media

Communication Channels/ Objectives	Advocacy Meetings	Outdoor Media (billboards, kiosks, posters)	Social Mobilization	Media (Print, TV)	Social Media	Interpersonal Communication
Awareness and information	+++	++++	+++	++	++++	++
Vaccine Risk Communication	+	++	+	++	++	+++
Crisis Communication	-	-	-	++	-	++++

Immunization communication plans are developed at district and state levels once a year by the State/District Mass Education and Information Officer / IEC officer or consultant and supported by the DIO. A template for RI communication planning has been shared with all states and districts (**Annexure 18**). The following are imperative in the making of a communication plan:

Communication Plan Template

1. Situation analysis and a review of current communication plan and strategies
2. Setting of objectives based on evidence-based research on the current methods
3. Defining target audience (primary and secondary)
4. Defining a media mix that would disseminate the programme message in the proposed catchment area (IPC through advocacy and social mobilization, mass media for general awareness, outdoor media as a reminder medium, and social media for creating buzz and reaching out to the young population)
5. Pre-testing of communication messages
6. Campaign seasonality (i.e., when to launch the communication campaign, keeping in view the immunization program, other considerations, social and political).
7. Evaluation and feedback (impact analysis of communication for course correction, future lessons)
8. Budget and division among various media keeping in view reach access and impact

11.2.2 Vaccine Risk Communication

One of the barriers to demand generation and a major cause of dropouts is the refusal to get children vaccinated due to the discomfort suffered after vaccination. Mild fever, local pain and swelling, irritability, reduced feeding, etc., are expected reactions. These are self-limiting and disappear within two-three days even if no treatment is provided. Syrup paracetamol helps in providing relief along with local cold compresses. However, parents invariably worry about the side effects and may not be willing to get their child vaccinated again. There are other misperceptions based on rumours and myths which often dissuade parents from going in for vaccination, like an unfounded belief that vaccination may cause impotency. This may not be explicitly expressed by parents for fear of offending frontline workers and vaccinators.

Interpersonal Communication

Health workers, ASHAs and AWWS are the first point of contact for information on immunization by beneficiaries and caregivers. Interpersonal communication is one of the most effective ways of conveying to beneficiaries that the risk of suffering from minor side effects of vaccines is less than the risk of hospitalization, disability, and death in the case of not vaccinating children against vaccine-preventable diseases. IPC enables front-level workers (FLWs) to share correct information about immunization, respond to queries and questions, clarify myths and misconceptions, and motivate hesitant families to accept immunization services.

Stop the blame game, support health workers

Whenever a serious AEFI occurs, the police department should be urged to protect health worker against public outrage. The FLWs (including vaccinators) have to be protected from violence by the affected community members. A designated senior person needs to assure the aggrieved family expressing concern and empathy, of the action taken by the government to go into the cause of death/serious illness.

The FLWs including vaccinators need to themselves trust and support vaccinations. It is important to consult health workers, ASHAs and AWWs to understand their concerns regarding vaccine safety and to know where they lack knowledge.

Capacity Building of FLWs

Use the non-crisis period to empower frontline workers to enable them to share accurate immunization facts, respond to questions, clarify possible doubts, encourage families and communities to adopt healthy behavioural practices, including understanding the importance of immunization, risks faced by unimmunized and partially immunized children and availing timely vaccines. Build their capacity to engage with the community and practice inter-personal communication (IPC) skills by:

- Building their technical knowledge on vaccines, risks of common, minor AEFIs and VPDs
- Using BRIDGE training (Boosting Routine Immunization Demand Generation) for frontline workers to improve general communication skills, including listening, empathizing, counselling, group communication and negotiation skills as part of interpersonal communication (IPC) skills to improve RI demand generation and expansion.

Essentials of Risk Communication

While communicating with parents/caregivers who are delaying vaccination or are wary of exposing their minor children to risk, and common side effects following vaccinations, keep the following in mind:

1. Listen to what the caregiver is saying.
2. Understand local perceptions of the disease, injections, and the vaccine.
3. Keep key messages in mind. Use the appropriate key message for the particular clarification sought.
4. Make sure to communicate the benefits of vaccination.
5. Avoid technical terms and long words or phrases.
6. Anticipate counterpoints and prepare effective responses.
7. Provide a big picture on the safety of vaccines per say.

Engaging with Media

When there is no crisis, it is the best time to build a rapport with media personnel, especially those covering the health or development sector.

- Create and update a list of reporters with contact numbers and email addresses.
- Understand the requirements of the reporters and regularly provide them with information and news related to the latest health and immunization activities.
- Push for positive news stories related to immunization and other health programmes related to immunization such as child nutrition, maternal health, etc. to create a positive environment about immunization and encourage people to vaccinate their children.
- Create a media corner on the website and post all press releases and other videos regularly. Empirical research suggests that government website becomes a good source of information for media and communities, especially during crisis situations.
- Explain to them how the programme works and give them routine immunization fact sheets related to the district, state and national level. Organise workshops and field visits to session sites and cold chain points and show the mechanisms in place for safe vaccination.
- Monitor the media for reports from time to time.
- Train spokespersons to respond to media queries regarding AEFI, building rapport, ensure evidence-based reportage and a follow-up story on the incident.
- Engaging regional/language media which is trusted by marginalised and minority communities. It is only prudent not to create a communication vacuum as it will be soon filled by misinformation, gossip-mongering.
- Cite Multiple Sources: Ensuring that media cites multiple sources when reporting on AEFI. Normally there is a tendency to cite statements of parents, ignoring statements of CMO, independent experts etc.
- Evidence-based Reporting: Media should cite evidence where applicable (Data, medical reports, knowledge products etc).
- Ensure follow-up media report: Officials should be in regular touch with the media person to ensure that a follow up report is published.

Social Media Messaging

Use social media to spread positive messages regarding vaccines and immunization programme. Each social media platform has its own characteristics and user base. There should be a system for rigorous monitoring, tracking of rumours, myths and identification of rumour-mongers. After tracking, the focal point needs to be informed and updated with immediate alerts through the established chains of communication. Facebook pages, WhatsApp groups and official Twitter accounts of state and district health departments can be used to share positive messages/best practices. It is best if messages and GIFs and videos are created at the state level and shared with districts for dissemination. Each district should identify a focal person to maintain and circulate these messages regularly.

Other key points are:

- Spread Awareness: Seek support of media to spread awareness on Dos and Don'ts when going for vaccination (eg: to not vaccinate in case of fever etc)

- Avoid using scary caricatures which could lead to hesitancy
- Avoid sensationalism: Refrain from sensational reporting/headlines
- that could lead to panic
- Avoid religious undertones in reportage

Some of the dos for use of social media, when there is no crisis are as follows:

1. Messages, GIFs, and videos should be carefully crafted and pre-approved before these are shared on social media.
2. Ensure messages contain facts and are not speculative in nature
3. Photographs used depict proper/ideal vaccination practices
4. The language used is simple and non-technical and conveys the message appropriately
5. If personal photographs are being shared, take written permission from the concerned person to post them for social media messages.

Make sure of the following don'ts:

1. Do not use incorrect information or facts which cannot be verified
2. Do not use messages targeting a particular community, class or race
3. Do not use language which is offensive or defamatory
4. Do not name a particular vaccine brand or vaccine manufacturer
5. Do not give names and other personal information to any person in messages without the permission of the person.

Engagement with Radio

Radio is the main source of entertainment to the marginalized sections of society. Radio as part of the equity-focused communication strategy, has been used to create awareness and engage audiences in remote parts of the country for routine immunization, Mission Indradhanush and Measles Rubella campaigns. Engaging Radio Jockeys (RJs) has been found to be particularly effective in allaying fears of parents regarding AEFI and vaccination especially during campaigns such as the MR campaigns.

Capacity-building of Media Persons

In addition to swiftly and effectively responding to the AEFI queries of media, it is vital to help media persons provide balanced and evidence-based reporting by introducing them to online training courses such as Critical Appraisal Skills (CAS)[43]. Courses like these impart competencies to critically appraise health and public health-related information and encourages accurate reporting of AEFI cases and responding to media queries. A tool to assess a news report for quality and balanced reporting is available at **Annexure 19**.

11.2.3 Preparing Communication Plans for Crisis Situations

A crisis in immunization is an emergency situation which is a result of an unexpected series of events that pose a risk to the integrity or reputation of the routine immunization program, immunization services or vaccines. Such situations are usually brought on by negative

[43] https://agora.unicef.org/course/info.php?id=22296

attention from the media or community members and can include adverse events, legal disputes, accidents, or man-made disasters attributed (rightly or wrongly) to the program and government efforts. Often, crisis can be avoided through foresight, care, and training. If managed properly, the crisis will strengthen the program and boost public confidence. When a crisis occurs, it is crucial that the government respond quickly and responsibly to minimize harmful fallout.

The best time to prepare for a crisis is when there is no crisis. Developing a crisis communication plan involves a lot of preliminary preparatory steps. Once the crisis communication plan is prepared, it must be shared with all stakeholders. Constant monitoring is important to identify a crisis early and act according to the possible impact on vaccine trust.

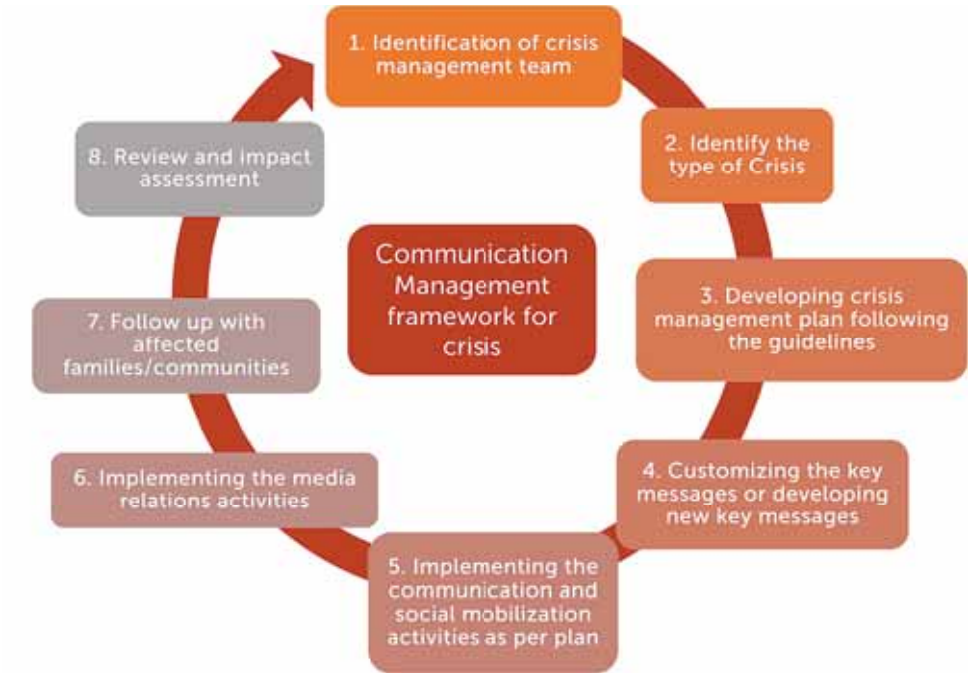
Developing a Routine Immunization Crisis Communication Plan

A crisis communication plan helps to respond to different types of crises in order to preempt a drop in public confidence in vaccination, and also possible disruptions to immunization programs. The crisis communication plan is prepared and managed by a communication crisis management group led by the DIO and the DMEIO/consultant responsible for developing the district immunization communication. Other officials such as the District Public Relations Officer, members of the district AEFI committee, etc., may be included in this group. The communication management framework for crisis situations is depicted in Figure 11.2.

The crisis management team at all such levels will be responsible for:

1. developing a crisis communication plan by listing potential crisis situations, grading them as per possible impact on vaccine trust, defining activities for each impact level, and responsibilities and tools to implement the communication plan.
2. identifying a situation which can trigger a crisis and taking appropriate action as per plan to manage it
3. assess the impact of the activities and review the plan.

Figure 11.2: Communication Management Framework for Crisis Situations



Key Messages

As discussed earlier, district-specific key messages and supportive messages need to be developed for events triggered by AEFIs. Some examples have been given in section 11.4. The key messages and supporting messages developed in English may be translated into the regional language. It is important to share these with key stakeholders who may be contacted by the public or the media.

Monitoring Mechanism

The plan should include details of a monitoring mechanism to alert when a potential crisis occurs. This may be a system for tracking news reports related to vaccines/vaccination programme appearing in newspapers, TV channels and also on social media every day. Any alert needs to be conveyed to the person designated to decide further action as per the crisis communication management plan. This person should, as indicated in the plan, coordinate to implement communication, social mobilization and media relations activities.

At the end of the crisis, review the impact of the activities in the plan. Assess critically the successes and failures to improve the crisis communication plan.

11.3 Crisis Communication Plan

11.3.1 Contingencies: Plan for the worst-case scenario for each type of crisis and develop a response for it.

Types of Crises:

The crisis communication plan[44] anticipates contingencies and crisis situations and lists activities related to communications to address/mitigate each situation. At the state and national levels, the crisis could be a controversy regarding the introduction of a new vaccine or changes to the immunization programme/vaccination schedule. The crisis can also be a critical public, media or scientific debate on vaccination. There may also be rumours or a misconception regarding vaccines/vaccination programme which has become viral on social media. Usually, the most common crisis a district is likely to face is an adverse event following immunization during routine immunization or an immunization campaign.

Prescribing Actions for Each Event Based on Impact Level

Having listed all kinds of possible crisis in the plan, the impact of each crisis/event on vaccine confidence should be assessed and calibrated actions should be listed. Some situations require informing the public early on using appropriate key messages. This may prevent the situation from escalating. Over-communicating about some minor events or events not really related to vaccination can cause unnecessary public concern and needlessly damage public confidence. An example is given in Table 11.2.

44. *Vaccine Safety Events: managing the communications response. A Guide for Ministry of Health EPI Managers and Health Promotion Units, WHO Regional Office for Europe, Copenhagen, Denmark, 2013.*

Table 11.2: Crisis Situation- Adverse Events Following Immunization

Impact level on vaccine trust	Description	Action
Low Impact	A child gets admitted after vaccination in hospital. Condition is stable. A newspaper runs the story the next day. There is no follow up by TV channels. Child gets discharged by evening, the day the new gets published in the newspaper.	Keep a close eye on the progress of the event. Be prepared to respond to these events with holding statements and trained spokespersons in case situation turns for the worse e.g. the child dies during treatment or a couple of other children are also admitted for treatment. Ensure AEFI surveillance system is alert and there are no other cases related to this case, which may have been missed. Keep in touch with media partners for any new information.
Medium Impact	Three infants are hospitalised after vaccination. Only one requires medical care, while the other two are kept for observation. A TV channel and a couple of local newspapers report on the event.	Do not communicate to a wider public audience yet. However, start preparing by: 1. Gathering more facts about the event 2. Engaging stakeholders, incl. spokespersons 3. Develop messages and share them with your allies, e.g. with stakeholders that may be contacted by media or public
High Impact	Two children die and three are hospitalised within 24 hours of vaccination in a village. Villagers blocked the nearby state highway and demand compensation. Almost all TV channels are showing visuals and covering the news continuously. Reporters of local newspapers are calling for details. The state health minister is also demanding a report on the event.	Respond immediately: 1. Gather your group of key media/ social media influencers 2. Gather more facts about the event 3. Understand the problem 4. Liaise with key stakeholders including spokespersons 5. Develop messages and share them with your allies, e.g. with stakeholders that may be contacted by media or public 6. Communicate externally

11.3.2 First Step Actions

Define communication actions that can be taken within a few hours of the event. Preparations may include developing:

- holding statements and key messages
- list of frequently asked questions with answers and key facts (e.g. on vaccine safety and vaccine-preventable diseases)
- preparing and keeping updated (every month) district AEFI response template (**Annexure 20**) and district or state RI factsheets
- identifying a primary spokesperson authorised to interact with media and secondary spokespersons (third-party experts who would be effective information sources for the media)
- media contact lists
- list of the key stakeholders you need to keep informed
- list of immediate information channels to all stakeholders (e.g. web, social media, e-mails, press release)
- vaccine reaction background notes.

In addition to the above, it is important to get as many details about the incident and keep updating the details as and when it is received. Once the vaccine details and details of the event are known, find out the expected reaction types using the vaccine reaction background note list.

Holding Statements

Prepare statements that can be used for initial media encounters in most types of vaccine crisis. Some examples are as follows:

1. Our deepest sympathy goes to the families of the child/ children. The following actions are being taken as of now: the child has been admitted to hospital, a team has already started investigations, other vaccine recipients are under close observation.
2. We have started the investigation of this unfortunate incident and doing our utmost to know the reasons behind it as soon as possible.

Decision-Making and Information Release Authority

Ensure that as soon as the plan is ready, it is approved by the competent authority at the district both for the SOPs, tools and financial aspects. The plan should have clearly defined information approval mechanisms during a crisis (who releases what, when, how) and procedures for information verification and expedited clearance. This is important as it speeds up the process of verification and approval of information regarding the event after collecting and compiling the information for quick release to stakeholders and media if required.

Roles and Responsibilities

Define clear roles and responsibilities during a crisis. Include guidance on coordination and collaboration between stakeholders representing different divisions and with specific areas of expertise (e.g., pediatricians, epidemiologists and communicators). Include a designated spokesperson who develops a clear plan on how activities will be coordinated, and who liaises with key internal and external stakeholders.

Information Sharing

Define how information will be shared with key stakeholders, media, and the public. Consider different routes to reach different audiences (e.g., face-to-face, announcements, web). Define mechanisms to ensure media inquiries are addressed as appropriate. Consider the media's needs i.e., deadlines, and ease of obtaining information. Ensure all media outlets have access to updated information and methods to get answers (e.g., post-press conference transcripts online).

Monitoring Public Opinion

Include guidance on monitoring public response (e.g., via social media and/or a hotline) to ensure an immediate response if warranted to any development, event or misperception.

Contacts

Prepare and continuously update lists with media contact information, including members of crisis response team's after-hours contact numbers, and other relevant stakeholders.

11.4 Preparing Key Messages

1. Messages should be well-prepared, accurate and empathetic.
2. Key messages should be shared with all stakeholders (including spokespersons) so that everyone sends out the same message!
3. Messages should ideally be tested on the target audience to determine comprehension and potential barriers to recommendations.
4. Use a message map to help prioritize and structure messages and identify gaps in knowledge. Message maps help to:
   (a) agree on messages
   (b) be precise with complicated topics
   (c) be consistent and repeat key messages
   (d) manage difficult questions and challenges
   (e) be more confident and convincing.

Use the format at **Annexure 21** to start defining three key messages and substantiate each key message with three supporting messages. An example of three Key messages and Supporting messages is given in Table 11.3.

Table 11.3: Example of Key & Supporting Messages

Key Message 1	Key Message 2	Key Message 3
Vaccines are safe.	Vaccines prevent diseases.	The risk of your child suffering from a vaccine preventable disease is more than the risk of minor side effects of vaccines.
Supporting message 1a	Supporting message 2a	Supporting message 3a
Serious side effects following vaccinations are very rare. Examples.....	Diseases such as tuberculosis, diphtheria, pertussis, measles, polio, etc. can lead to hospitalizations as they are life threatening, can cause disability and often, death.	Rates of fever following pentavalent vaccines Rates of local swelling and pain following pentavalent vaccines
Supporting message 1b	Supporting message 2b	Supporting message 3b
Minor side effects following vaccination such as fever, local pain and swelling, irritability, crying and reduced feeding will last for less than a couple of days.	There are _____cases of diphtheria and pertussis reported every year and ____ deaths are caused because of these two diseases.	Number of cases of diphtheria and pertussis in India Fatality rates of diphtheria and pertussis
Supporting message 1c	Supporting message 2c	Supporting message 3c
Syrup paracetamol will provide relief from the fever and pain.	Three doses of pentavalent vaccine will protect your child from diphtheria, pertussis, tetanus, hepatitis B and pneumonia and meningitis caused due to Hemophilus influenza b.	A couple of days of fever and local pain and swelling is nothing compared to the risk of getting infected, hospitalized, and dying due to pertussis and diphtheria

Other examples of key messages are as follows:

1. Adverse events following vaccination are very rare.
2. Most adverse events are coincidental and have no relation to the vaccination.
3. The occurrence of adverse events does not mean that vaccines are unsafe.
4. Minor adverse events such as fever, pain and swelling are common and expected and will disappear within two-three days.
5. If a child becomes severely sick following vaccination, the ASHA/AWW/ANM should be informed for advice and the child should be taken to the nearest hospital for treatment.

Once these key messages and supporting messages are created, these can be shared with medical officers, block extension educators, other health functionaries and also professional associations, to use it to advocate with "custodians" (keepers of good and positive relationships with the community) who are in regular touch with the community to make rigorous efforts in encouraging vaccinations, to prevent the community from losing confidence in vaccinations and reduce occasional negative public opinion related to immunization.

These messages can be used for advocacy with other local community leaders and panchayat functionaries, religious leaders and key influencers, workshops, mothers' meetings, community meetings, etc.; used while interacting with the media; considered while developing information material for mid-media activities - posters, banners, hoardings, leaflets, wall paintings, miking, etc.; and also for preparing messages, posts and tweets for social media (design local and context-specific messages, GIFs, video bytes, etc.

It takes a lot of effort, patience, and resources to maintain the trust and goodwill of the community and media in the vaccination programme must be sustained. If the community and the media have trust in the health department to be a source of factual and credible information during the 'good' times, they will be more receptive to information and explanations during 'crises'.

11.5 Communication Activities During a Crisis

11.5.1 Interpersonal Communication

An immediate response in case of a crisis is to engage with the affected families/community and establish a rapport with them as early as possible. A health worker or medical officer with good communication skills should be nominated as a focal person to empathize with the care-givers and the community. Local influencers and leaders should be identified, and support sought from them to reach out to the affected family/families. Timely dissemination of a consistent set of easy-to-understand key messages to concerned families and communities will help to ease their anxiety. The district should immediately ensure proper medical treatment is arranged for those requiring hospitalization. Arrangements should be made for transportation and referral to hospitals and free treatment.

11.5.2 Engaging the Media During a Crisis

Follow the AEFI media management protocol when the media takes interest in an AEFI. The AEFI response protocol is a set of actions which are recommended to be implemented in a time bound manner to keep the media informed of the AEFI, gives facts regarding the case, the response of the health department, status of the affected person and what steps are being taken to prevent the recurrence of the event. The objective is to reach out and respond appropriately to the media, killing speculations or at least make sure that the scientific and program point of view is conveyed, creating confidence in the program.

The protocol also creates a 'standard procedure for communicators' to make the process faster. It lists SOPs or activities required to resolve the AEFI crisis and enables the government spokespersons. Other tools that can be used are the 'AEFI response templates', state RI factsheets and ready reckoners to help them with 'uniform messaging' while communicating with the media. It also sets up a 'timeframe for response' that will ensure that the media gets access to correct information in time, mitigating the crisis. The protocol also lists the role of partners and how best they can help while keeping the messages uniform.

All state immunization spokespersons are to be notified immediately about any media report and query from all administrative levels using the latest means of communication e.g., by email or phone. A summary of the SOPs is given in Table 11.4.

Table 11.4: Actions Recommended for Responding to Media Queries

District Level	
Authority	**Action Points**
District Immunization Officer (DIO)	When an AEFI gets reported, proactively get information on the case and note down the details. If unable to investigate, get in touch with the MO in the field for first-hand information. This will help get credible and timely information to the media, dismissing speculations and building trust through a credible source. Respond to a media query by sharing factual and non-speculative information which can be verified. The information should not trivialize the event. The message should convey that the government is aware of the AEFI and is investigating it and is also tracking developments in the field. If the media continues to pursue the event or it is felt that some journalists may misinterpret the situation or message, then it is better to give out a written response/press release (**Annexure 20**). Share the written response with all the concerned officials at the Immunization Office at state and national level SIMULTANEOUSLY (who might get media queries as well). Responses to media have to be time bound. Factual and timely information will kill speculations. ***Recommended Timelines to be Followed*** • A press release/response statement within 6-12 hours (using AEFI response templates that will be circulated) • If queries persist, State Spokespersons to respond at the earliest. • If a CRISIS at district level escalates to the State level media, a Press release should be made at the earliest preferably by Spokesperson.

District Immunization Officer (DIO)	Get back to the media with more information/developments as promised. Also direct the media to talk to trusted non-government specialist doctor/ expert to support queries on vaccine safety. Keep the expert informed and motivated to speak. Groups like IAP, IMA and other technical spokespersons in the states should be identified for responses as and when possible. Ensure there are no conflicting messages by the spokespersons. In case the media has not included the District/State Immunization Office's version of the AEFI, then immunization officials should actively reach out to the reporter who wrote the news and give the correct information and the health department's perspective. If media reports continue to not include the health department's version, then ensure a statement is prepared and mailed to the reporter or the newspaper office or put it up on the website. If the reporter or the newspaper is doing negative stories about the program without asking for government perspective, then a statement with factual information on the AEFI cases, status of investigation should be prepared and mailed to the editor of the newspaper requesting for publishing the facts/or clarifying the issue. Depending on how active the media is in the district, the editors and journalists of various media should be sensitized about AEFI reporting and surveillance.
State Level	
Authority	**Action Points**
State Immunization Officer (SEPIO)	When media queries arise, follow a similar response protocol. When an AEFI gets reported, proactively get information on the case and note down the details. If unable to investigate, get in touch with the DIO or MO in the field, to access first-hand information. This will help get credible and timely information to the media dismissing speculations and building trust in a credible source. When a media query arises, share factual information which can be verified. Talk to the media, dismissing speculations and give out the message that the state is investigating and tracking the AEFI case/s. The information should be non-speculative without trivializing the event. The message should include that the government is aware of it, is investigating the said AEFI and is also tracking the developments in the field. Respond with a statement (**Annexure 20**). If required, also talk to the media and give verbal answers. Follow the timeline for response according to the urgency of the media queries.

REMEMBER

The next time there's a media query on AEFI, we

- have an authorized government spokesperson, who is updated with information
- respond to media queries with factual information
- use AEFI response templates as and when need be
- adhere to timelines for responding
- keep higher-ups informed about media queries

There are different ways of reaching out to the media to help communicate with the public. A few of them are listed below:

- Press Statement
- Press Release
- Press Conference
- Press Interview
- Clip of the spokesperson uploaded on the website

Please refer to **Annexure 22** and **Annexure 23** for details of when and how to use these.

11.5.3 Social Media and Crisis Communication

When there is a crisis situation, it is always better not to give out information regarding the specific event in the social media. It is very likely that any information shared in one WhatsApp group can be easily forwarded to other groups unknowingly by any member of the group.

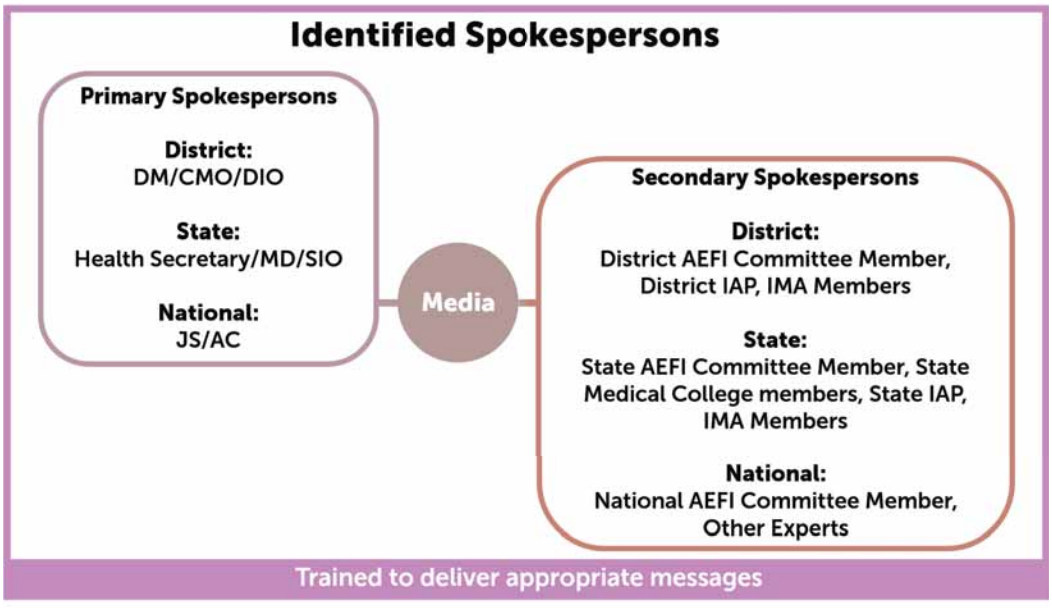
If information is received on Twitter or Facebook regarding an adverse event, convey that the information has been noted and conveyed to the concerned person for further action which includes providing medical help and investigation of the case to know the cause and preventive actions, if any. Do not engage with anyone posting negative posts/comments about vaccine safety on social media as it gives traction and contributes to making the message viral.

Continue to send out positive messages about vaccine safety. Special positive messages contextualizing the event can be created, carefully vetted before approval and dissemination.

11.5.4 Managing an Adverse Event Crisis

If effective communication is exercised at all levels, it can avert the possibility of a crisis. The information flow from identified speakers is depicted in Figure 11.3.

Figure 11.3: Information Flow-Identified Spokespersons



If at all a crisis occurs, it can be managed by following the steps given below in Table 11.5. Remember that some of these activities need to be done beforehand in anticipation of a crisis.

Table 11.5: Managing an Adverse Event Crisis

Serious /Severe AEFI such as Death/Hospitalization/Cluster		
Level of Intervention		***Communication Action Points***
Community Level	Health Worker	• Inform the Medical officer/District Immunization Officer immediately. • Meet the family - parents/ caregivers and empathise with them. • Listen to what the parents/public is saying patiently. • Ask some village elders, religious leaders to accompany you when you go to meet the family. • Follow-up with the family again after one or two days and ensure about their well- being. • Respect their personal space/privacy.
PHC/Block Level	Medical Officer	• Arrange for treatment immediately. Arrange an ambulance for referral. Ensure that the case is adequately treated at the hospital it is referred to. • Meet the family with a trusted health worker. • Take control of the situation and reassure the community without appearing judgemental. • Keep the family and community informed with facts and accurate information. • If the case is yet to be investigated, and information is scanty, inform the community that the matter is being looked into and the facts will be out in 'x' time (specify it). • Understand the perspective of the family/ community and disseminate appropriate messages. • Verify facts regarding the event and inform DIO and superiors.
District Level	District Immunization Officer (DIO)	• Ensure treatment of the cases at the hospital. • Start investigations immediately and prepare the report. • If required, involve the district AEFI committee members in the investigation. • Understand the community's perception towards immunization and whether there is dip in confidence in vaccination programme. • If required, contact supportive opinion leaders, to discuss the situation and find possible solutions and way forward. • Identify support groups from within the community who could be positive role models to convince the community that vaccines are safe and vaccination continues to be beneficial for children. • Respond to negative media questions with positive answers.

State Level	State EPI Officer	• Do not bombard with visits; respect their private space/ privacy. • Share feedback on the progress of investigations with community representatives. • Review media reports for tonality and accuracy. • Prepare a list of print and electronic media journalists covering health at state level with their contact details • Identify spokespersons and orient them on how to respond to the issue • Disseminate at appropriate times a consistent set of easy-to-understand key messages to concerned families and communities to help allay anxiety and reaffirm faith in the health system. • Organize orientation workshops and deliberations for journalists. This will help identify, in advance, the questions or concerns that journalists specifically have. • Organize orientation workshops and field visits for journalists. This will help them achieve a better understanding of immunization advantages as well as complexities of an immunization programme. • Involve school teachers to help in sending across correct information/ message(s) to parents/caregivers of children and educate them.
National Level	Government official/ National AEFI Committee	• Track tonality and accuracy of media reports; • Prepare a list of print and electronic media journalists covering health at state level with their contact details • Identify spokespersons and orient them on how to handle media queries • Organize visits for journalists, so as to enable them have a better understanding of the immunization program and government efforts. • Participate in 'talk shows' on the issue to clarify the negative picture and appease further rumours from rising.

Summary

- Crisis communication related to adverse events following immunization should be part of regular routine immunization communication plans.
- Frontline workers and medical officers in PHCs should be trained on inter-personal communication skills as this is the most effective medium to communicate during crisis.
- Engaging with print and TV media should be a continuous and a part of the planned activity.
- Social media messaging has its own rules. It is important to have a person familiar with social media to handle it.
- Other available communication media may be explored as per the purpose of engagement, the key messages to be communicated, the target audience and reach of the media.
- Developing Key messages and Supporting messages is an important activity for regular and crisis communication.
- Developing crisis communication plans is a group activity involving all stakeholders with tailor made responses actions for specific situations and based on the level of impact on trust on vaccines and the programme.
- A media response protocol should be in place for responding to media during crisis. All respondents and stakeholders should have a copy of the plan and should know their exact roles and responsibilities.
- The crisis communication plan should be developed proactively when there is no crisis.

12 Quality Management System for Improving AEFI Surveillance

Setting standards as per quality benchmarks is the first step towards the implementation of quality management system. Robust standards make the processes transparent, institute responsibility and accountability, and improve efficiency and safety. Regular assessment against the standards helps to identify gaps and action taken to reduce these gaps will incrementally improve the quality.

One of the key strategies for improving AEFI surveillance at different levels is to implement a Quality Management System (QMS) within the surveillance programme. It will also include the provision of a third-party certification audit of the system. Under the National Health Mission (NHM), a quality assurance programme is being implemented to improve the quality of services being provided in public health facilities. A multi-pronged strategy under this is already in place which includes institutionalisation of the quality assurance programme, formation of quality teams at different levels, implementation of a system of continuous assessment of health facilities using the National Quality Assurance Standards (NQAS)(https://qps.nhsrcindia.org/quality-assurance-framework/operational-guidelines), capacity building of all functionaries for meeting the NQAS norms and lastly NQAS certification of the health facilities. The performance of health facilities is monitored regularly through verifiable processes and outcome indicators. The National Quality Assurance Standards (NQAS) are internationally accredited by ISQua (International Society for Quality in Healthcare).

To support quality interventions, State Quality Assurance Committee (SQAC) and District Quality Assurance Committees (DQAC) are functional at the state and district level, respectively. These committees are supported by the teams that have trained quality professionals in all the states & UTs.

The National Quality Assurance Standards for AEFI surveillance[45] were developed in 2016 to initiate the quality management system in the AEFI surveillance programme. The national-level AEFI Secretariat has been certified with NQAS AEFI standards since 2016. QMS for AEFI surveillance was piloted in two districts each in two states and based on the experience, the guidelines for NQAS for AEFI surveillance were finalised for rollout across the country.

12.1 Overview of NQAS for AEFI surveillance

The quality assurance standards for the AEFI surveillance programme are in line with the national AEFI Surveillance and Response Operational Guidelines, issued by the Ministry of

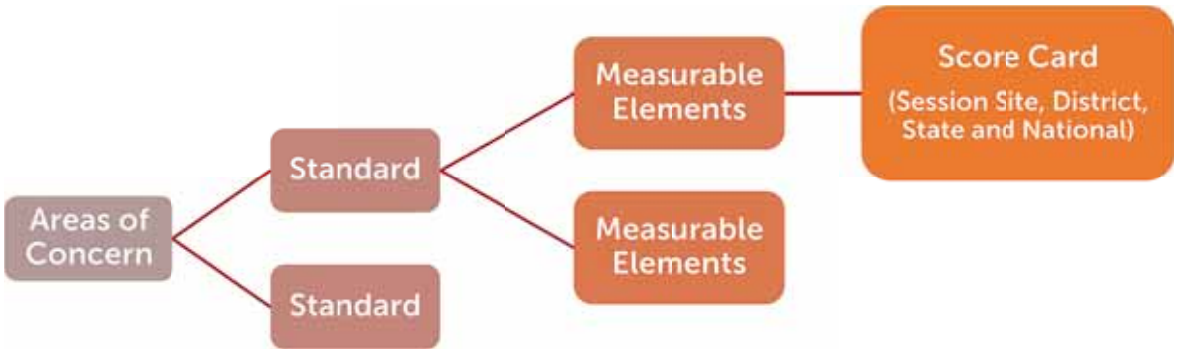
45. *https://main.mohfw.gov.in/sites/default/files/National%20Quality%20Assurance%20Standard%20AEFI%20on%2022-11-16%20B.pdf;*

Health & Family Welfare, Government of India. Based on key processes of the programme, the following eight areas of concern have been established:

(a) Notification and reporting
(b) Investigation
(c) Causality assessment
(d) Operational management
(e) Communication
(f) Convergence
(g) Monitoring & feedback.

There are four checklists for each level of implementation of AEFI surveillance – national, state, district and PHC/session site. Each checklist is divided into different areas of concern. For each area of concern, there are related measurable elements (ME) against defined standards (Figure 12.1).

Figure 12.1: Areas of Concern, Standards, Measurable Elements & Score Card



Measuring elements help in generating evidences and information through following assessment methods:

(a) Observation
(b) Staff interview
(c) Beneficiary interview and
(d) Record review

There are three types of assessments – internal, peer and external. For a specific level, the same checklist is used for all types of assessments. Based on the analysis of evidence, a score is generated against each of the ME after every assessment. Checklist-wise, area of concern-wise and standard-wise scorecards can be generated at the end of every assessment. Scores of external assessments, rendered by qualified external assessors lead to certification, provided other conditions have been met.

Details of the area of concern, standards, and assessment methodology have been provided in the National Quality Assurance Standards for AEFI surveillance program guidebook (2016). The assessment tools of NQAS are subject to revision whenever there is any change/update in the operational guidelines for AEFI surveillance and response.

12.2 Implementation of QMS for AEFI Surveillance

Quality standards for the AEFI surveillance programme will be applicable at all levels starting from the session sites to the national level. Key activities for implementation of QMS for AEFI are enumerated below:

- Orientation meetings of state and district quality assurance managers and immunization programme managers for QMS in AEFI.
- Development of state implementation plan for the QMS in AEFI surveillance.
- Preparation of budget based on districts selected for the implementation.
- The budget should be projected by the states for provisions under state PIPs under appropriate FMR code.
- Notification regarding inclusion of state and district quality assurance unit members in AEFI committees at the state and district levels.
- Finalisation of SOP templates at the state level, issue of instructions for developing quality policy and quality objectives, dissemination of SOPs, checklists, etc. to districts with clarity on roles of different stakeholders in the implementation process of QMS for AEFI surveillance.
- Operationalisation of QMS in states - orientation of staff, development of SOPs, quality policy, quality objectives, conducting internal assessment, gap assessment and closure, coordinating the peer assessments, external assessment and certification for State and session sites etc.
- Operationalisation of QMS in districts-training of district-level staff, training of PHC MO in charge, development/customisation of SOPs, quality policy, quality objectives, conducting internal audits, gap assessment and closure, peer assessments, etc.
- Operationalisation of QMS in PHCs and session sites-orientation of staff, development/ customisation of SOPs, quality policy, quality objectives, conducting internal assessment, gap assessment and closure, peer assessments, etc.

Quality experts from the existing state and district quality assurance committees/units have been nominated as members/ special invitees of state and district AEFI committees to guide and support the implementation of QMS. Each state implements NQAS for AEFI Surveillance with support from the AEFI Secretariat, NHSRC and state Quality Assurance committee/unit. All districts and municipal corporations should initiate its implementation in their area of responsibility. Protocol for the internal, peer and external assessments under the programme, and certification criteria are listed in Implementing guidebook of Quality Management System for AEFI surveillance in states and districts. Programme Guidelines (https://itsu.org.in/wp-content/uploads/2022/10/Quality-Management-System-for-AEFI_Guidebook-1.pdf), the checklists can be downloaded from https://itsu.org.in/adverse-event-following-immunization-resource-materials-ri-3). To support the implementation in the states and districts, an implementation guide has been developed, which can be downloaded from: https://qps.nhsrcindia.org/sites/default/files/2022-03/9.%20Implementation%20Guidebook%20of%20Quality%20Management%20System%20for%20AEFI%20Surveillance.pdf

Certification under NQAS for QMS-AEFIs is given to states/UTs after external assessment of the state/UT. This can be done only if 50 percent of all districts in the state score more than 70 percent in peer assessments. Therefore, all states and UTs should strive to implement QMS in all districts simultaneously and get certified as soon as possible. The budgetary norms have been created for each activity of QMS under FMR code RCH 4-Immunization-S.No. 32-SSRE of National Health Mission-Programme Implementation Plan.

Summary

- One of the key strategies to improve AEFI surveillance at different levels is to implement a Quality Management System (QMS) for AEFI surveillance.
- Quality standards for the AEFI surveillance programme will be applicable at all levels starting from the session sites to the national level.
- The QMS will be implemented jointly by immunization programme managers and quality assurance experts at state and district levels.
- The National Quality Assurance Standards for AEFI surveillance contains indicators, benchmarks and assessment tools for quality in AEFI surveillance at session site/PHC, district, state and national levels.
- Assessments (internal, peer and external) are done based on eight areas of concern with standards and measurable elements.
- QMS-AEFI certification will be given for an entire state/UT and not for individual facilities or districts.

13 National Regulatory Authority for Vaccines

13.1 National Drug Regulatory Authority

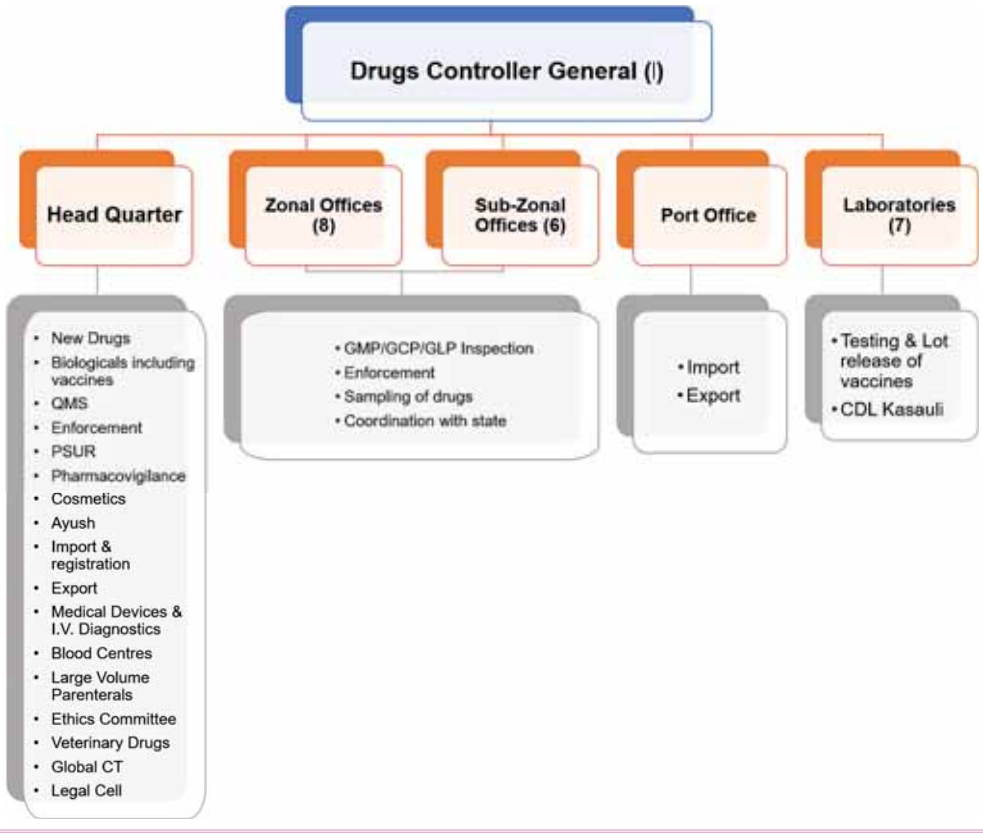
13.1.1 Central Drugs Standard Control Organization (CDSCO)

The CDSCO under Directorate General of Health Services (DGHS) in Ministry of Health and Family Welfare (MoHFW), Government of India, is the National Regulatory Authority (NRA) of India.

All vaccines are defined as "New Drugs" and regulated under "The New Drugs & Clinical Trial Rules, 2019" & "The Drugs & Cosmetics Act, 1940" and "The Drugs & Cosmetics Rules, 1945"

CDSCO[46] is headquartered and located at New Delhi and has eight zonal offices, six sub zonal offices, thirteen Port offices and seven laboratories spread across the country (refer to figure 13.1). Each state and union territory has its own drugs control department under the respective state government and is responsible for monitoring the manufacture, sale and distribution of drugs within their respective jurisdiction.

Figure 13.1: Organogram of CDSCO and its Laboratories



46. https://cdsco.gov.in/opencms/opencms/en/Home

The common mandate for CDSCO (National Regulatory Authority) and all state and union territorial drugs control authorities is to ensure the safety, efficacy and quality of "Drugs" including vaccines and biologicals as per the Drugs & Cosmetics Act 1940 and various rules under it, the Drugs & Cosmetics Rules 1945, New Drugs Clinical Trial Rules 2019 and the Medical Devices Rule, 2017. Under the Drugs and Cosmetics Act, 1940 the licenses for manufacturing and sale of drugs are granted by the Drugs Control Department in a state / union territory.

Specifically, in relation to AEFI and vaccine pharmacovigilance, AEFI Cells have been established in the CDSCO Headquarters and all zonal offices with designated focal persons. The AEFI Division of CDSCO(Hq) coordinates with the IPC, Immunization Division, MOHFW and the AEFI cells located in various zonal offices for the various AEFI reported in the field.

13.1.2 Central Drugs Laboratory, Kasauli

CDL (Kasauli)[47] is the National Control Laboratory for testing of immunobiologicals (vaccines and antisera) meant for human use in India and also for vaccines produced indigenously and imported for the domestic market, immunization programme of the Government of India and export. This laboratory has been NABL accredited in the field of biological and chemical testing since 2008. CDL, Kolkata[48] is the national statutory laboratory under the central government for testing implicated samples of AD syringes/ reconstitution syringes and Vitamin A for standard sterility and physical parameters.

13.1.3 Pharmacovigilance Programme of India (PvPI), IPC Ghaziabad

The Indian Pharmacopoeia Commission (IPC)[49] functions as the National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI) and the Materiovigilance Programme of India (MvPI) for medical devices and diagnostics safety reporting. It is an autonomous institution under Ministry of Health and Family Welfare, Government of India, entrusted with the functions of formulating and regularly updating the standards of drugs required for treatment of diseases prevailing in India. It publishes the Indian Pharmacopoeia (IP), an official regulatory document for the quality standards (in the form of monographs and general chapters) of drugs and National Formulary of India. The IP Reference Substances (IPRS) are also provided by the IPC to the stakeholders. Apart from above, IPC has also been entrusted with responsibilities of operationalizing Pharmacovigilance Programme of India (PvPI). The PvPI was operationalized in July 2010 with a mission to reduce the risks associated with the use of medicines in Indian population.

13.1.4 National AEFI Secretariat, ITSU-MoHFW

The Immunization Division, MoHFW has established a National AEFI Secretariat with four zonal AEFI consultants to support AEFI surveillance. The AEFI Secretariat supports the National AEFI Committee and four sub-committees (causality assessment, investigation, laboratory and media) and the Immunization Division to make informed decisions about improving

47. https://cdlkasauli.gov.in/CDL_KASAULI/Homepage
48. https://cdsco.gov.in/opencms/opencms/en/Departments/Lab/CDL-Kolkata/
49. http://www.ipc.gov.in/PvPI/pv_home.html

AEFI surveillance and ensuring vaccine safety. In addition to causality assessments, the AEFI Secretariat also implements the signal management functions as a part of the regulatory process.

13.2 Roles and Responsibilities of Stakeholders

13.2.1 CDSCO

The roles and responsibilities of the CDSCO as per the Drugs and Cosmetics Act, 1940, and Rules framed under it, as follows:

1. Approval of new drugs, clinical trials, BA/BE study and centre.
2. Import registration and licensing.
3. Licensing of blood banks, large volume parenteral, vaccines, antisera, r-DNA products, veterinary products & medical devices.
4. Laying down the standards for drugs and controlling the quality of imported drugs in the country, thereby ensuring the safety, efficacy and quality of all vaccines in India.
5. Coordinating activities of State Drug Control Organizations by providing expert advice for uniformity in the enforcement of the Drugs and Cosmetics Acts & Rules made there under.
6. For taking appropriate regulatory decisions and actions of the basis of the Pharmacovigilance Programme of India (PvPI), National Coordinating Centre (NCC) at IPC, Ghaziabad, and the AEFI surveillance programme of the Immunization Division of the Ministry of Health and Family Welfare (MOHFW), New Delhi.
7. To ensure that all importers and manufacturers of any "new drug" (including vaccines) should have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction (ADR) report to CDSCO as per the Fifth Schedule of The New Drugs and Clinical Trial Rule, 2019.
8. For taking appropriate regulatory decisions and actions on the basis of analysis of the PMS, PSUR, AEFI data based on the recommendations of the expert committee.

The Fifth Schedule of The New Drugs and Clinical Trials Rules, 2019, is reproduced below:

I. Post-Marketing Assessment of New Drug

1. When a new drug is approved for marketing, assessment of safety and efficacy of the drug are generally based on data from a limited number of patients, mainly studies like clinical trials which are conducted in controlled settings. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.
2. In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the drug shall be closely monitored and post-marketing assessment of its benefit-risk profile shall be carried out once it is marketed.
3. An organisation intending to import or manufacture any new drug for sale or distribution

shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction report to the Central Licensing Authority emerging from the use of the drug imported or manufactured or marketed by the applicant in the country.

4. The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.
5. Post-marketing assessment of new drug may be carried out, in different ways as under.

Phase IV (Post-Marketing) Trial

Phase IV (post-marketing) trial includes additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trials will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population.

In such trials, the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines.

In such a study, the study drug may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug free of cost, to the satisfaction of the Central Licencing Authority and the ethics committee.

Post-marketing Surveillance Study or Observational or Non-Interventional Study for Active Surveillance

Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licencing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert. In such studies, the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs are already approved for marketing.

Post-marketing Surveillance through Periodic Safety Update Reports

As part of post-marketing surveillance of new drug the applicant shall furnish periodic safety update reports (PSURs) in accordance with the procedures as follows:

(a) The applicant shall furnish periodic safety update reports (PSURs) in order to:
   (i) Report all relevant new information from appropriate sources
   (ii) Relate the data to patient exposure
   (iii) Summarise the market authorisation status in different countries and any significant variations related to safety
   (iv) Indicate whether changes shall be made to product information in order to optimise the use of product

(b) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one periodic safety update reports. Within the single periodic safety update reports separate presentations of data for different dosage forms, indications or separate population need to be given.

(c) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years - the periodic safety update reports need to be submitted annually. Central Licensing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licencing authority within fifteen days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(d) New studies specifically planned or conducted to examine a safety issue should be described in the periodic safety update reports.

(e) A PSUR should be structured as follows:
   (i) Title Page
   (ii) Introduction
   (iii) Current worldwide marketing authorisation status
   (iv) Actions taken in reporting interval for safety reasons
   (v) Changes to reference safety information
   (vi) Estimated patient exposure
   (vii) Presentation of individual case histories
   (viii) Studies: Summaries and findings of significant safety findings from clinical trials during the reporting period, non-interventional Studies, non-Clinical Studies, literature etc.
   (ix) Other information (if any).
   (x) Overall Safety Evaluation: This section of periodic safety update reports should capture the overall safety evaluation of the drug based upon its risk benefit evaluation for approved indication.
   (xi) Conclusion
   (xii) Appendix

13.2.2 Central Drugs Laboratory, Kasauli

Responsibilities of CDL, Kasauli are as follows:

1. In case of an AEFI, CDL, Kasauli is the appellate laboratory for testing and analysis of vaccines for physical aspects, sterility, abnormal toxicity and biochemical identities and submit the report to CDSCO and the Universal Immunization Programme.
2. Quality control of immunobiologicals (vaccines and sera) imported, produced indigenously for domestic use or for exports.
3. Advice to NRA on technical matters and interaction with manufacturers for improvement in the quality of immunobiologicals including post approval changes.
4. Scrutiny of manufacturer's Summary Lot Protocols and evaluation of CMC Module-III of manufacturing and quality control of immunobiologicals.
5. Pre-licensing and post-licensing testing for assuring consistency of production.
6. Development, evaluation, establishment and implementation of testing procedures.
7. Review of reports on quality defects & provision of advice on withdrawals of vaccines and sera.
8. Research and development in the field of quality control of immunobiologicals.

13.2.3 Pharmacovigilance Programme of India, IPC

The IPC functions as the National Coordination Centre (NCC) for Pharmacovigilance Programme of India since 15th April 2011. It has steering committee working group, signal review panel, quality review panel and core training panel to spearhead various activities of PvPI. PvPI also encourages healthcare professionals and consumers to report adverse drug reactions as and when they occur, to the nearest ADR Monitoring Centre of PvPI. NCC-PvPI has a network of more than 800 ADR Monitoring Centres across India and is under continuous expansion process.

The objectives of National Coordination Centre for Pharmacovigilance Programme of India are as follows:

- Create a nationwide system for patient safety by ensuring drug safety
- Identify and analyze new signals from the reported cases for medicines
- Analyze the benefit-risk ratio of marketed medications
- Generate evidence-based information on safety of medicines
- Support regulatory agencies in the decision-making process on use of medications
- Communicate safety information on use of medicines to various stakeholders for preventing/minimizing the risk

Based on the contribution of PvPI-IPC, it has also been designated as WHO Collaborating Centre (CC) for Pharmacovigilance in Public Health Programmes and Regulatory Services and has been continuing its services.

The PvPI team at AMCs will be responsible for collecting the serious and non-serious AEFIs and reporting to NCC. All AMCs functioning under PvPI coordinate and share the serious AEFI with the District Immunization Officer (DIO) & State EPI Officer (SEPIO) immediately through Serious AEFI Case Notification Form. The serious Individual Case Safety Reports (ICSRs) of AEFI received at NCC-PvPI from AMCs are immediately communicated to AEFI Secretariat &

Pharmacovigilance Division of CDSCO for further action at their end, whereas non serious ICSRs are communicated regularly. The regulatory intervention, advisory and alerts related to vaccine are communicated to AEFI Secretariat for information and further necessary action, if any.

PvPI works with several institutes and National Health Programmes such as Adverse Event Following Immunization (AEFI) at Immunization Technical Support Unit (ITSU) under the Immunization Division of MoHFW, Govt of India, National TB Elimination Programme (NTEP), National AIDS Control Programme (NACP)-National AIDS Control Organization (NACO) and National Vector Borne Disease Control Programme under National Centre for Vector Borne Disease Control (NCVBDC). It also works with pharmaceutical industries and professional bodies in the interest of promotion and protection of public health.

Several tools and methods have been introduced by the PvPI to collect ADRs through ADR Monitoring Centres (AMCs) which are spread across the country, toll-free helpline number 1800-180-3024, android-based mobile app "ADR PvPI" and via email at pvpi.ipc@gov.in.

The details of ADR monitoring centres in India can be obtained from the following web link: www.ipc.gov.in; https://ipc.gov.in/images/842_AMC_Details_As_on_date_03.08.2023_for_website.pdf

13.2.4 Immunization Division/AEFI Secretariat

While reporting and investigations are done by the districts, causality assessments are conducted at the state and national levels. At the national level, the causality assessment sub-committee conducts causality assessment of severe and serious AEFI cases and presents their observations and results to the National AEFI Committee for approval. The approved causality assessment reports are then submitted to the MOHFW and shared with the CDSCO for further action, if required.

A signal review panel for vaccines with representation from the CDSCO and pharmacovigilance partners analyses the AEFI database and other reports related to vaccine safety. The PSURs are also evaluated for safety signal and benefit-risk assessment as part of vaccine vigilance. The recommendations of the signal review panel are shared with the CDSCO for regulatory action.

The details on coordination of CDSCO (HQ)/ State drug controller/Zonal drug controller, PvPI (AMCs) with immunization programme at various level is given in Table 13.1.

Drug inspectors are deputed by the concerned State Drug Control Department and the concerned CDSCO (zonal) office as members of the district AEFI committee which investigates AEFIs with the DIO. The drug inspectors are responsible for collecting samples of implicated vaccine vials and other concomitant drugs, diluents, etc. after a decision has been made to do so by the district AEFI committee in consultation with the State Immunization Officer. The collected vaccine samples are sent to CDL, Kasauli for testing and analysis.

Table 13.1: Coordination of Stakeholders with Immunization Programme

National Level	• Sharing CRFs every week by the AEFI Secretariat • Sharing results of causality classification of reported AEFI cases for further regulatory actions • Representative of CDSCO is part of special investigation team • PSUR review committee meetings are attended by AEFI Secretariat • CDSCO, PvPI and CDL Kasauli are members of the National AEFI Committee, Signal Review Panel and the monthly pharmacovigilance partners' meetings • Joint capacity building programmes are conducted to ensure each stakeholder is informed of processes and activities of other • Sharing of AEFI reports collected from AMCs by NCC-PvPI • AEFI Secretariat is involved in training of pharmacovigilance associates of AMCs
State Level	• Zonal CDSCO office supports the state AEFI committee • State drug controller is a member of the state AEFI committee • Provides support and is part of special investigation team • Nodal officers / technical associates of ADR monitoring centers are members of State AEFI Committee
District Level	• Drug inspectors (DI) are members of District AEFI Committees • DI are involved in AEFI investigation and support DIO in specimen (vaccine and logistics) collection, whenever required. • Nodal officers / technical associates of ADR monitoring centers are members of District AEFI committee • AMC reports all serious/severe AEFI cases to the DIO.

Stakeholders at various levels- CDSCO (HQ)/ State drug controller/Zonal drug controller and PvPI (AMCs)

Figure 13.2 schematically represents the coordination among pharmacovigilance stakeholders.

Figure 13.2: Coordination among Pharmacovigilance Stakeholders

The CDSCO, CDL Kasauli, Pharmacovigilance Programme of India (under IPC) and the Immunization Division (AEFI Secretariat) are jointly assessed by international experts of the World Health Organization periodically. The objective of the NRA assessment is to ensure that all the stakeholders considered part of the NRA for vaccines, achieve the benchmarks for specific indicators for regulatory oversight for vaccines including for the vigilance function as defined in the WHO National Regulatory Authority (NRA) Global Benchmarking Tool (GBT) **(please** refer: https://iris.who.int/bitstream/handle/10665/341243/9789240020245-eng.pdf?sequence=1**).**

Summary

- Central Drugs Standard Control Organization (CDSCO) is the National Regulatory Authority (NRA) for drugs including vaccines.
- The State Drug Controller is a member of the state AEFI committee. The drug inspector, under the state drug controller is a member of the district AEFI committee and is responsible for lifting vaccine and logistics samples during AEFI investigations.
- CDL, Kasauli is the National Control Laboratory for testing of vaccines.
- The Pharmacovigilance Programme of India (PvPI) under the Indian Pharmacopoeia Commission (IPC) coordinates Adverse Drug Reaction Monitoring Centres (AMCs) in medical colleges and large hospitals.
- Stakeholders at all levels have specific roles and responsibilities and work together to report and investigate AEFIs, share and analyse data to identify vaccine safety issues.
- The signals are assessed by the Signal Review Panel for vaccine safety at AEFI Secretariat and regulatory recommendations are implemented by CDSCO.
- All stakeholders considered part of the National Regulatory Authority (NRA) are jointly benchmarked by World Health Organization periodically with benchmarks and indicators for core regulatory functions including for the Vigilance function, as part of the WHO Global Benchmarking Tool.

14 Safety Surveillance for Adult Vaccinations

The Universal Immunization Programme of the country primarily targets pregnant women (with Td vaccines) and children to reduce mortality and morbidity due to vaccine-preventable diseases (VPDs) among them. **Annexure 24** provides details of vaccines in the UIP schedule. There is a thrust to improve coverage among adolescents due to an epidemiological shift in the incidence of VPDs toward older age groups following high vaccine coverage in younger age groups.

14.1 Vaccinations in Adults

Adults need vaccines because immunity wanes with ageing. Some comorbidities in older age predispose individuals to VPDs and related complications. TT vaccines are administered to adults after injuries and before surgical procedures. According to the UIP schedule, Td vaccines are administered during pregnancy. A large number of rabies vaccine doses are also administered following animal bites. Additionally, yellow fever vaccines are given before international travel to certain destinations. The uptake of influenza vaccines, hepatitis B vaccines, vaccines to protect against Typhoid, and other respiratory infections, etc. is poor as these are costly and available in the private sector. India has experience of vaccinating adults with JE vaccines in certain districts endemic for JE. After smallpox vaccinations, COVID-19 vaccines are the most administered vaccines in adults in India at a large scale. Please refer to chapters 2 and 3 to understand how COVID-19 vaccines work and the safety characteristics of COVID-19 vaccines used in India. It is expected that in the future, there will be an increase in the uptake of adult vaccinations. Therefore, it is imperative to work on widening the scope of AEFI surveillance to capture adverse events following the use of vaccines in adults.

14.2 AEFI Surveillance for Adult Vaccinations

The reporting channels, formats for reporting AEFIs in adults, processes for investigation and causality assessment and timelines remain the same as for AEFI cases in children, even for vaccines used in the private sector. The reporting and investigation forms are now modified to include collection of information relevant to adults with AEFIs.

Reporting and recording: Strengthening AEFI surveillance for adult vaccinations requires sensitizing health workers and medical officers regarding the possibility of AEFIs in adults. It also requires expanding the reporting network to cover tertiary care hospitals and sensitizing doctors of the departments of medicine, neurology, cardiology, respiratory medicine, obstetrics and gynaecology, etc. Doctors should enquire about and record the history of any vaccination in adults in case records and report identified AEFIs. A private practitioner or health care facility can inform/notify an AEFI case to the concerned government MO/DIO. Thereafter, the case should be investigated by the district health authorities.

Investigation: Investigations of AEFIs in adults require special consideration due to the possibility of various comorbidities and risk factors which may not be present in children. Besides details of current illness, clinical history eliciting all comorbidities and risk factors, records of previous illnesses and treatments including OPD visits, family history etc. should be collected. Conducting post-mortems should be strongly encouraged in all death cases reported as AEFIs.

Verbal autopsy forms for adults (different from children) should be administered in all death cases even if a post-mortem has been conducted. Medical specialists, neurologists, cardiologists, respiratory medicine specialists, and gynaecologists should also be members of the district AEFI committees so that their inputs are considered while assigning a valid diagnosis to AEFI. Experts from other specialities may be included in the investigation as per the requirement of a case. Please refer to **Annexure 11** for a verbal autopsy form specially designed for use in investigating deaths reported as AEFIs in adults.

Causality assessment: Causality assessments of adult AEFI cases also require the involvement of these specialists (medical specialists, neurologists, cardiologists, respiratory medicine specialists, and gynaecologists) as members of the state and national AEFI committees. If required, other specialists may be specially invited to discuss the diagnosis and causality of certain cases.

14.3 Recommendations for Adult Vaccinations

For adults, some vaccines are recommended by groups of experts / professional associations to protect certain groups of adults at risk of exposure to a particular disease due to illnesses/ comorbidities/ risk factors or travel to endemic areas, etc. **Annexure 25** has details of some of these vaccines and indications for their use in adults.

14.4 Recommendations for Vaccination during Pregnancy

Due to ethical considerations, pregnant women are excluded from clinical trials. Evidence on vaccine safety in pregnant women has been generated by following up women who were thought to be not pregnant at the time of vaccination but were found to be pregnant later on. Even if a pregnant woman gets a vaccine that is contraindicated during pregnancy, no interventions (such as MTP, etc.) are required. The risks of vaccination during pregnancy are largely theoretical. Ideally, in case of a planned pregnancy, an adult woman should have received all recommended vaccines at least a month before pregnancy.

Killed vaccines and toxoids are safe in pregnancy. Vaccines recommended during pregnancy are Td/ Tdap and inactivated influenza vaccine to protect the pregnant mother and the infant. One dose of influenza vaccine is recommended from 26 weeks onwards. (Federation of Obstetric and Gynaecological Societies of India (FOGSI). Vaccination in women 2014. https://www.fogsi.org/wp-content/uploads/2015/11/vaccination_women.pdf). Influenza vaccines

are not part of the UIP and are administered in private sector. Live vaccines (BCG, OPV, measles-containing vaccines, JE, varicella, yellow fever, live influenza vaccines, and others) are contraindicated in pregnancy. Some vaccines which are usually not recommended for pregnant women, can still be administered to them under special circumstances when the benefit of vaccination of the pregnant woman or foetus/child is much more than the risk of adverse outcomes. Examples of these are when pregnant women have to travel to areas endemic to yellow fever or where there is an outbreak of Japanese encephalitis. Rabies vaccination in pregnancy for post-exposure prophylaxis is not a contraindication as rabies is a nearly 100% fatal disease (National Guidelines on Rabies Prophylaxis. National Rabies Control Programme. National Centre for Disease Control, MOHFW, GOI (2015). Hepatitis A (inactivated whole cell viral), Hepatitis B (inactivated subunit viral) vaccines, and meningococcal vaccines can be given to pregnant women with risk factors or under special circumstances.

According to the Operational Guidelines of the National Viral Hepatitis Control Program, 2018, institutional delivery of HBsAg-positive pregnant women is mandatory to prevent transmission to the child by giving birth dose Hepatitis B vaccine and Hepatitis B immunoglobulin.

Summary

- Most of India's experience in vaccinating adults is Td for pregnant women (UIP) and mass campaigns - JE vaccination in certain endemic areas and COVID-19 vaccinations. Vaccinations are also administered for rabies (for animal bites), Hepatitis B, influenza, etc.
- Coverage of adult vaccinations is expected to increase in the coming years. There are certain indications for vaccinating adults based on risk factors, comorbidities, etc., recommended by clinicians and authorities.
- The existing AEFI surveillance guidelines (formats, timelines, reporting channels, etc.) will be applicable for reporting, investigating and causality assessment of AEFIs following adult vaccinations.
- It is important to widen the network for reporting AEFIs through sensitization of doctors likely to treat these adults (medical specialists, neurologists, cardiologists, obstetrician-gynaecologists, etc.)

15 Strengthening Safety Surveillance for New Vaccine Introduction

15.1 Introduction

New vaccines are vaccines which are introduced in the country for the first time on a mass scale usually through the Universal Immunization Programme either in campaigns (such as MR campaign for rubella) or directly in the national immunization schedule e.g. rotavirus vaccine or inactivated polio vaccine.

A vaccine can be introduced in the country only after the national drug regulator (CDSCO) licenses the vaccine for use. CDSCO looks at the results of the clinical trials and assesses the benefits and risks associated with each vaccine before granting a license to manufacture or import it. The clinical trials must show that the vaccine is safe and effective. Before a vaccine is granted authorisation in India, the drug regulator needs to be satisfied that the vaccine will be safe and efficacious in the Indian population keeping in mind ethnicity and other genetic variations. The regulator may ask for bridging studies which are smaller and may be of shorter duration even if adequate international data is available. Additionally, the drug regulator can ask for Phase IV (Post-Marketing Trial), Post-Marketing Surveillance or observational or non-interventional study for active surveillance including for Adverse Events of Special Interest (AESI)[50].

The decision to include a new vaccine in the national immunization schedule is based on many considerations, including disease burden, disease severity and its potential complications, availability and affordability of vaccines, safety and suitability of available vaccine products for national programmes, the feasibility of its introduction and the cost-benefit analysis based on all of the above factors. Once it is decided to include a new vaccine, several steps are needed to ensure its successful introduction and sustainable use[51].

New vaccine introductions in the country involves multiple consultative processes and assessments prior to introduction. The National Technical Advisory Group on Immunization (NTAGI) is the body of experts which studies the epidemiological evidence, cost benefit analysis and many other points before recommending the introduction of a new vaccine in the UIP against a particular disease. An important consideration before including a vaccine in the UIP schedule is whether manufacturers can ensure regular and long-term supply in adequate volumes to the programme. Other activities conducted before the actual introduction include assessment of the readiness of the states and districts, need assessment and sensitisation of potential beneficiaries, availability of additional cold chain space, training of health staff, changes to monitoring and reporting formats, etc.

50. https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublic_NoticesFiles/Regulatory_guidelines_for__development_of_Vaccine_20.9.20.pdf
51. https://www.who.int/europe/activities/introducing-new-vaccines-into-national-routine-immunization-programmes

When vaccines are administered during campaigns, a large number of doses are administered in a very short time period. There is also a heightened awareness of the public, the health care workers and the media towards any adverse events that may be temporally linked to vaccination[52]. Managing adverse events reported following the introduction of a new vaccine is also an important activity and stakeholders involved in AEFI surveillance need to be oriented on this.

One of the major challenges faced when a new vaccine is introduced is the non-availability of a complete safety profile of the vaccine. Safety data available at the time of introduction is usually limited to clinical trial data. The regulators determine that the potential benefits outweigh the potential risks of the vaccine and a final analysis will include all safety data accumulated from phase 1, 2 and 3 studies. After approval of a vaccine, stringent follow-up is essential to monitor vaccine safety in routine use through phase IV Post-Marketing Surveillance and other studies.

Some of the indigenously developed vaccines such as Rotasiil or Rotavac when used for the first time in India, will have only clinical trial data. Post-marketing safety data of high quality may not be available at the time of introduction. On the other hand, vaccines like Pneumococcal vaccines were introduced in the UIP after they had already been in use in other countries for a long time. They have a good safety record based on data from countries with stringent regulatory oversight including strong vaccine safety surveillance systems. Ebola virus vaccines were used in Africa following approval based on compassionate use. In the case of COVID-19 vaccines, Emergency Use Authorization was initially granted by the drug regulator at the national level, and long-term follow-up of subjects under clinical trials was continued even after EUA was granted.

COVID-19 vaccines were new vaccines which were granted Emergency Use Authorisation/ approval for restricted use in emergency situation[53] due to the threat of the pandemic. These vaccines underwent modified but rigorous processes of safety assessment prior to their approval. In order to further ensure monitoring of safety and efficacy, the drug regulator directed manufacturers to put in place systems for post-marketing assessment of vaccines in accordance with the general guidelines specified in the Fifth Schedule of the New Drugs and Clinical Trials Rules, 2019.

15.2 Active Safety Surveillance

Well-functioning regular passive AEFI surveillance systems can identify rare, serious adverse events following the introduction of new vaccines. Passive Adverse Events Following Immunization (AEFI) surveillance system captures minor, severe, and serious adverse events and can provide trends and potential signals requiring further studies and assessments. However, this system cannot capture all adverse events following vaccinations due to the passive nature of reporting.

52. https://covid-19pharmacovigilance.paho.org/img/recursos/60a82278b5257e63c783bebe6.pdf
53. https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/notice15april21.pdf; https://pib.gov.in/PressReleaseIframePage.aspx?PRID=1711979

Active surveillance involves proactively obtaining and rapidly analyzing information to verify safety signals identified through passive surveillance or to detect additional safety signals that may not have been reported as adverse events to passive surveillance systems. Active AEFI surveillance may be undertaken through

1. Cohort Event Monitoring: Information on vaccine exposure is known from the beginning in a defined population-at-risk cohort. This cohort is then followed up over time for the occurrence of disease or events of interest. This is done usually for new vaccines. Actual incidence rates of vaccine adverse events can be calculated using Cohort Event Monitoring, in addition to absolute risk and relative risk estimates. Cohort Event Monitoring is particularly useful to assess the risk of adverse events in vulnerable populations such as pregnant women, children, adolescents, etc.

2. Analysing Electronic Health Records (EHR): This is usually done using electronic health records from insurance or healthcare databases which have diagnosis which are coded as per standards such ICD-10. Such databases are used for calculating prevalence and incidence rates year-wise as well as producing stratified estimates by age, sex, socio-economic deprivation and geographical region. These can be used to provide almost real-time incidence or background rates (expected rates) for any diagnosis or event and precise inputs for policymaking. Countries with advanced EHR systems such as UK, USA, Australia are already using these methods for estimation of disease burden/background rates.

3. Sentinel surveillance for specific events: Sentinel sites are set up in carefully chosen large hospitals in which targeted events are identified. All identified events are followed up for fulfilling case definitions, vaccine exposure, reaction to treatment and outcome, etc. Additional information is gathered for each individual to look for risks, etc.

Many COVID-19 vaccines were built using novel platforms or platforms rarely used on a mass scale. Based on the experiences from existing/past vaccines or vaccine platforms on which COVID-19 vaccines were developed, WHO's SAGE (SPEAC/CEPI) identified 23 potential AESIs. AESIs are predefined medically-significant events that have the potential to be causally-associated with a vaccine product and that need to be carefully monitored and confirmed by further specific studies. A subset of AESIs for low- and middle-income countries (LMICs) have been identified to prioritize enhanced vaccine safety surveillance. For COVID-19 vaccines in India, Immunization Technical Support Unit (ITSU) under the guidance of a Technical Advisory Group (TAG) has undertaken a multi-centric AESI sentinel surveillance study involving 16 medical colleges across India to understand the risk of occurrence of select AESIs following COVID-19 vaccines. From the list of 23 AESIs shortlisted by SPEAC/CEPI, ten AESIs were studied.

A similar active surveillance study for routine immunization has been conducted by INCLEN in India. The Multicentric Active AEFI Surveillance Study (MAASS) used a sentinel AEFI surveillance network of public and private tertiary care hospitals to monitor the occurrence of pre-

defined clinical conditions (cases and controls) among hospitalized under 2-year-old children for known serious and severe AEFIs (seizures, thrombocytopenia, and acute encephalitis syndrome) and identify any potential linkages with vaccines.

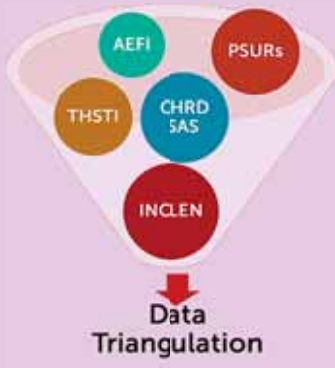
15.3 Signal Detection and Communication

A strong vaccine safety signal management system is required to identify any potential safety event requiring assessments and studies. A Signal Management Framework for Adverse Event Following Immunization (AEFI) as part of the overall vaccine safety surveillance system for India has been operationalised by the AEFI Secretariat. A Signal Review Panel assessed the risk-benefit of vaccines, beginning with COVID-19 vaccines. The same system is being utilised to identify potential vaccine safety signals for regular and newer vaccines. Please refer to details in Chapter 10.

Other methods can be used to identify and study vaccine safety signals when signal management systems are not well-developed. An example is the analysis of pooled vaccine safety data from different sources. Under the Smart Safety Surveillance (Triple S) Programme, for studying the risk of intussusception following newly introduced Rotavac vaccine in India, available data related to intussusception from various sources such as the government's passive AEFI surveillance system, the data from AMCs under PvPI, the PSURs shared by manufacturers to the drug regulator and special safety/impact studies conducted by various research organizations were pooled and triangulated to characterize the safety profile of Rotavac vaccine.

Triangulation of Safety Studies on Rotavac Vaccine in India

The Smart Safety Surveillance (SSS) approach is a collaborative effort among national regulatory authorities, the national immunization programme in India and other key vigilance stakeholders for vaccines to strengthen pharmacovigilance capacity.



The Immunization Division and the CDSCO coordinated the synthesis of safety data from all sources (routine surveillance data and systematically designed studies) for Rotavac, a new vaccine used for the first time in India before other countries. The data, leveraged from multiple sources, was triangulated and a White Paper was developed, which provided reassurance on the safety. It was decided that a similar approach, which brings together all stakeholders in immunization safety, should be considered to assess the safety of other newer vaccines.

From a public health perspective, timely and effective communication of signal information to relevant stakeholders is the linchpin upon which effective pharmacovigilance practice rests. Understanding the balance between the benefits and risks of vaccination is essential to ensure informed and adequate public health decision-making. The community (vaccine recipients, relatives) need to be informed of safety issues in such a manner that the benefit and risk of vaccinations are properly conveyed without causing alarm and enabling them to make informed choices of whether to vaccinate or not. Key decision-makers need to be informed to enable them to make regulatory and programmatic decisions, as needed. Medical professionals should be informed to enable them to suspect, identify, manage and report such issues. AEFI committees should be trained for effective investigations (district level) and causality assessments (state and national levels).

15.4 Preparing for New Vaccine Introductions

New vaccines may be introduced by following the due regulatory and programmatic processes (in the case of routine vaccines) or through emergency use authorisation (as for COVID-19 vaccinations). Preparations are required for both situations to enable improved monitoring of vaccine safety.

Some of the preparatory activities are described below:

1. Estimation of event-specific background rates in the population

A way to generate estimates of event-specific background rates in the population is to conduct literature review and meta-analysis. In the absence of such literature, specific surveillance studies can be done in the preparatory phase prior to vaccine introduction to estimate the same. Access to electronic health records of large insurance or health databases can help in getting this information on an almost real-time basis. Comparisons can be made on event-specific incidence before and after the introduction of a new vaccine. These may not be accurate but can give an estimate.

2. Improving ease of reporting of all AEFIs (including minor events)

The reach of SAFE-VAC, a web-based portal for reporting serious/severe cases of adverse events following immunization by the districts, may be expanded to allow any healthcare worker including doctors in medical colleges, private and public tertiary hospitals to report adverse events to the system. Integration of SAFE-VAC with UWIN is the first step towards this objective.

3. Establishing active AEFI surveillance systems for routine immunization

A functional active sentinel surveillance for AEFIs following routine vaccinations (to elicit potential signals and to conduct further studies on possible signals) can ensure availability of trained personnel and systems in place to study AESIs or identify signals following new vaccines. Developing active AEFI surveillance systems in the country is also a recommendation of the National Regulatory Authority (NRA) assessment conducted by WHO in 2017.

4. Strengthening vaccine signal management processes

Using statistical tools and software for analysis of vaccine safety datasets to identify potential signals quickly with accuracy, sensitivity and specificity will make signal management faster for routine vaccinations as well as when a new vaccine is introduced.

5. Capacity building, monitoring & supervision and communication

To avoid occurrence of preventable AEFIs such as immunization errors, vaccinators, cold chain handlers, supervisors and immunization programme managers should undergo training before introduction of new vaccines. Healthcare professionals need to be trained to handle and administer different vaccines, specifically newly introduced vaccines with different storage conditions or administration techniques as compared to conventional vaccines to avoid immunization errors which are preventable (please refer to Chapter 8, section 8.3). It is essential that vaccines are used in accordance with the indications, contraindications, dosage, storage conditions, reconstitution procedures etc. outlined in the package insert. Each vaccine from a different manufacturer may have different specifications and failure to comply with them can result in AEFI. Stringent monitoring of vaccination sessions and vaccine and logistics storage conditions is required to ensure guidelines and SOPs are properly followed. Corrective actions need to be taken immediately. The mechanisms should be in place to provide urgent feedback or communication for immediate corrective actions.

Summary

- The AEFI surveillance system needs to be strengthened for new vaccine introductions under routine as well as Emergency Use Authorization conditions.
- Active AEFI surveillance systems/studies supplement the vaccine safety information available through the regular AEFI surveillance system which is passive in nature.
- Cohort event monitoring and sentinel surveillance for specific events or AESIs are some active surveillance methods which can be planned and implemented for new vaccine introductions.
- Increasing the reporting of adverse events (including minor adverse events) will strengthen the confidence in signal management outcomes.
- The capacity to quickly generate estimates of event-specific rates in the population is essential to evaluate the benefit-risk of vaccines
- Developing active AEFI surveillance systems for routine vaccines will ensure trained personnel and tertiary care hospital networks are in place to enable quick modifications for active AEFI surveillance for new vaccines (routine and under EUA).
- Communicating risk-benefit assessments to different stakeholders in a timely, transparent and non-alarming manner enabling informed decision-making is key to maintaining trust and acceptance of new vaccines.

Annexures

Annexure 1: Types of Vaccines

UIP Vaccines

S. no.	Vaccine	Strain	Type of Vaccine
1	BCG	Mycobacterium Bovis	Live attenuated
2	Hepatitis B	HBs antigen	Subunit protein based
3	OPV	Polio virus type 1 and 3	Live attenuated
4	IPV	Polio virus type1, type 2 and type 3	Killed
5	Diphtheria	Diphtheria toxoid	Toxoid
6	Whole cell pertussis	Bordetella pertussis	Killed
7	Tetanus	Tetanus toxoid	Toxoid
8	Haemophilus In fluenzae B	HiB-PRP-TT	Conjugate
9	Rotavirus	Rotavirus G9P11 (Rotavac) Five serotypes G1,G2, G3, G4, G9 (Rotasiil)	Live attenuated
10	Measles	Edmonston-Zagreb measles virus	Live attenuated
11	Rubella	Wistar RA27/3 rubella virus	Live attenuated
12	Pneumococcal	Pneumococcal 10 valent	Conjugate
13	Japanese encephalitis	Japanese encephalitis virus – SA-14-14-2, Kolar-821564XY	Killed

Non-UIP Vaccines

S. no.	Vaccine	Strain	Type of Vaccine
1	Acellular pertussis	Bordetella pertussis	Subunit protein based
2	Rabies	Rabies virus	Cell cultured
3	Mumps	Jeryl Lynn strain of mumps virus	Live attenuated
4	Varicella zoster	Oka/Merck strain of Varicella zoster virus	Live attenuated
5	HPV	HPV 16, 18, 6 and 11 type virus	Subunit protein based
6	Typhoid	Vi polysaccharides of Salmonella typhi Ty2	Conjugated, killed, polysaccharide
7	Influenza	Influenza virus - H1N1, H3N2, Yamagata, Victoria	Killed, live attenuated
8	Yellow fever	YF 17D strain	Live attenuated
9	Meningococcal	Meningococcal Group A, C, W135 and Y Conjugate	Conjugate
10	Hepatitis A	Hepatitis A H2 strain HAV antigen (TZ84 strain)	Killed Inactivated
11	Cholera	Vibrio Cholerae 01, 0139	Killed, live attenuated

Annexure 2: Brighton Collaboration AEFI Case Definitions

S. no.	Adverse Event	Reference Article for Case Definition
1.	Abscess at injection Site	Abscess at Injection Site: Case Definition and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. Katrin S Kohl, Leslie Ball, Jane Gidudu, Sandra Jo Hammer, Scott Halperin, Paul Heath, Renald Hennig, Jerry Labadie, Edward Rothstein, Anne Schuind, Frederick Varricchio, Wikke Walop, Brighton Collaboration Local Reactions Working Group for Abscess at Injection Site. Vaccine 2007 Aug 1; 25(31):5821-38. doi: 10.1016/j.vaccine.2007.04.057. Epub 2007 May 11. PMID: 1754048
2.	Acute Aseptic Arthritis/ Aseptic Arthritis/Arthralgia	Acute aseptic arthritis: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. Woerner A, Pourmalek F, Panozzo C, Pileggi G, Hudson M, Caric A, Abraham S, Varricchio F, Velasco C, Oleske J, Bauwens J, Bonhoeffer J; Brighton Collaboration Acute Aseptic Arthritis Working Group. Vaccine. 2019 Jan 7; 37(2):384-391. doi: 10.1016/j.vaccine.2017.08.087. Epub 2018 Oct 17.PMID: 30342899 Arthritis and arthralgia as an adverse event following immunization: A systematic literature review. Panozzo CA, Pourmalek F, Brauchli Pernus Y, Pileggi GS, Woerner A, Bonhoeffer J; Brighton Collaboration Aseptic Arthritis Working Group. Vaccine. 2019 Jan 7;37(2):372-383. doi: 10.1016/j.vaccine.2018.06.067. Epub 2018 Nov 28. PMID: 30502066.
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54.	Spontaneous Abortion and Ectopic Pregnancy	Spontaneous abortion and ectopic pregnancy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data Rouse CE, Eckert LO, Babarinsa I, Fay E, Gupta M, Harrison MS, Kawai AT, Kharbanda EO, Kucuku M, Meller L, Mallett Moore T, Subelj M, Kochhar S, Tavares-Da-Silva F; Global Alignment of Immunization Safety in Pregnancy (GAIA) Abortion Work Group; Brighton Collaboration Abortion Working Group. Vaccine. 2017 Dec 4;35(48 Pt A):6563-6574. doi: 10.1016/j.vaccine.2017.01.047. PMID: 29150062; PMCID: PMC5714431.
55.	Swelling at or near Injection Site	Swelling at or near injection site: case definition and guidelines for collection, analysis and presentation of immunization safety data. Kohl KS, Walop W, Gidudu J, Ball L, Halperin S, Hammer SJ, Heath P, Varricchio F, Rothstein E, Schuind A, Hennig R; Brighton Collaboration Local Reaction Working Group for Swelling at or near Injection Site. Vaccine. 2007 Aug 1; 25(31):5858-74. doi: 10.1016/j.vaccine.2007.04.056. Epub 2007 May 11. PMID: 17548132

56.	Systemic Lupus Erythematosus	Systemic Lupus Erythematosus: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Hersh, A. O., Alarcón, G. S., Bonetto, C., Pernus, Y. B., Kucuku, M., Santuccio, C., Živković, S., & ; Bonhoeffer, J. Vaccine. 2016 Dec 12;34(51):6572-6581. doi: 10.1016/j.vaccine.2016.09.031. Epub 2016 Nov 2. PMID: 27816371
57.	Thrombocytopenia	Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, Pool V, Riise-Bergsaker M, Tapiainen T, Varricchio F; Brighton Collaboration Thrombocytopenia Working Group. Vaccine. 2007 Aug 1; 25(31):5717-24. doi: 10.1016/j.vaccine.2007.02.067. Epub 2007 Mar 12.PMID: 17493712 Companion Guide: Thrombocytopenia
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60.	Unexplained Death	Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, Kohl KS, Lewis EM, Meyer C, Nelson T, Sandbu S, Schlaud M, Schwartz A, Varricchio F, Wise RP; Brighton Collaboration Unexplained Sudden Death Working Group. Vaccine. 2007 Aug 1; 25(31):5707-16. doi: 10.1016/j.vaccine.2007.02.068. Epub 2007 Mar 12.PMID: 17408816

61.	Vaccine Associated Enhanced Disease (VAED)	AESI Case Definition Companion Guide Vaccine-associated enhanced disease (VAED) Law, B. (2022). AESI Case Definition Companion Guide Vaccine-associated enhanced disease (VAED) https://doi.org/10.5281/ZENODO.7260748
62.	Vasculitis	IgA vasculitis (Henoch-Schönlein): Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data. Woerner A, Rudin C, Bonetto C, Santuccio C, Ozen S, Wise RP, Chandler R, Bonhoeffer J; Brighton Collaboration IgA Vasculitis (Henoch–Schönlein) Working Group. Vaccine. 2017 Mar 13;35(11):1559-1566. doi: 10.1016/j.vaccine.2016.09.024. Epub 2016 Dec 26. PMID: 28034474.
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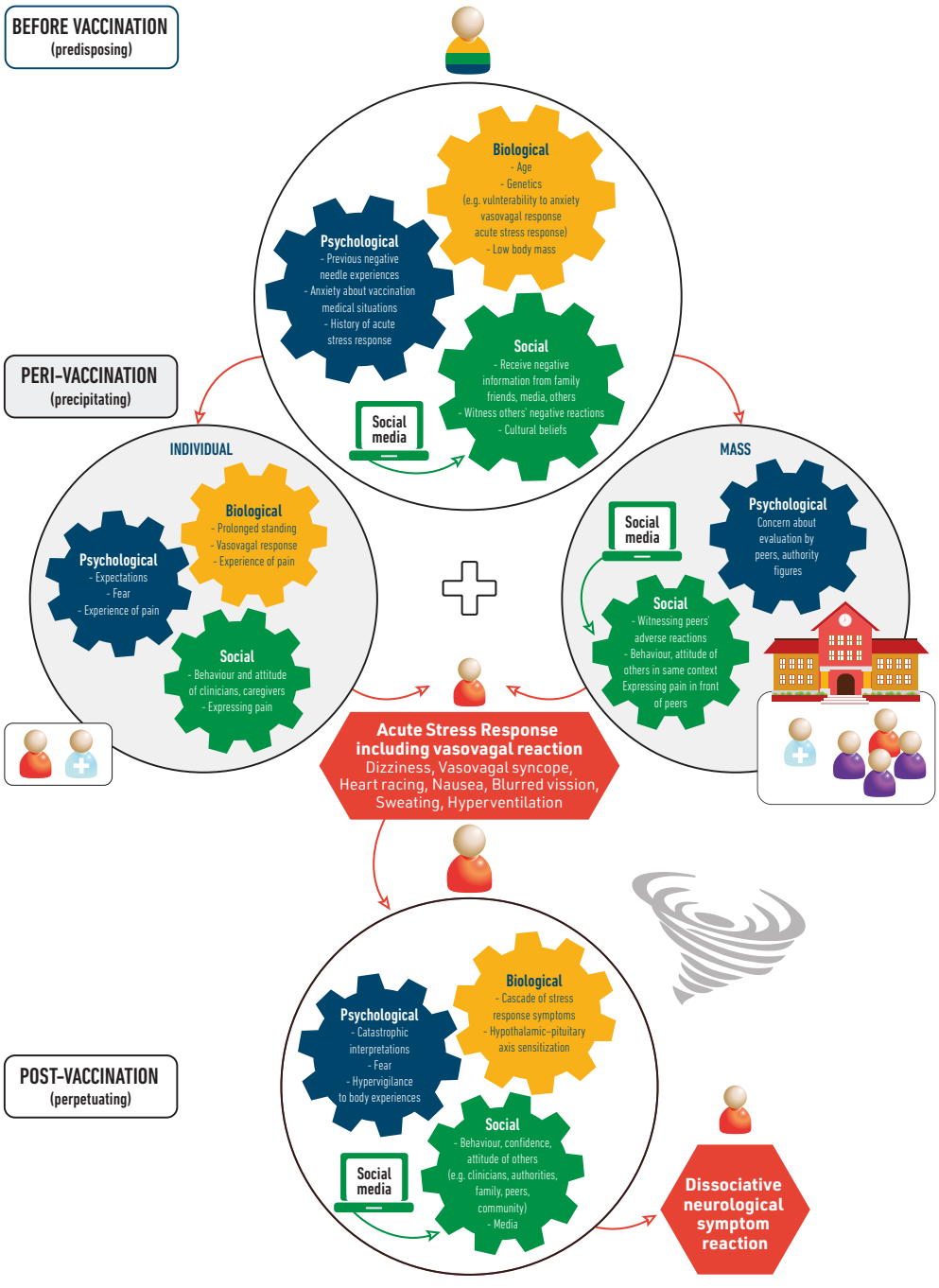
64.	Wheeze	Acute wheeze in the pediatric population: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Katz MA, Marangu D, Attia EF, Bauwens J, Bont LJ, Bulatovic A, Crane J, Doroshenko A, Ebruke BE, Edwards KM, Fortuna L, Jagelaviciene A, Joshi J, Kemp J, Kovacs S, Lambach P, Lewis KDC, Ortiz JR, Simões EAF, Turner P, Tagbo BN, Vaishnavi V, Bonhoeffer J; Brighton Collaboration Wheeze Working Group. Vaccine. 2019 Jan 7;37(2):392-399. doi: 10.1016/j.vaccine.2017.01.083. Epub 2017 May 5. PMID: 28483201.

Annexure 3: Biopsychosocial Conceptualization of ISRR

The figure below depicts the biopsychosocial conceptualization of Immunization Stress-Related Response (ISRR). This model shows the complex interplay among biological, psychological and social factors.



	Biological	Psychological	Social
Before vaccination (Predisposing):	• Age • Genetics (e.g. vulnerability to anxiety, vasovagal response, acute stress response) • Low body mass	• Previous negative needle experiences • Anxiety about vaccination • Medical situations • History of acute stress response	• Receive negative information from family, friends, media, others • Witness others' negative reactions • Cultural beliefs
Peri-vaccination (precipitating): Individual	• Prolonged standing • Vasovagal response • Experience of pain	• Expectations • Fear • Experience of pain	• Behaviour and attitude of clinicians, caregivers • Expressing pain
Peri-vaccination (precipitating): Mass		• Concerns about evaluations by peers, authority figures	• Witnessing peers' adverse reactions • Behaviour, attitude of others in same context • Expressing pain in front of peers
Post-vaccination (perpetuating):	• Cascade of stress response system • Hypothalamic pituitary axis sensitization	• Catastrophic interpretations • Fear • Hypervigilance to body experiences	• Behaviour, confidence, attitude of others (e.g. clinicians, authorities, family, peers, community) • Media

For details refer to Section 3.3.4

Reference: Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress- related responses following immunization. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO (https://iris.who.int/bitstream/handle/10665/330277/9789241515948-eng.pdf?sequence=1).

Annexure 4: Guidelines on Use of Syrup Paracetamol (post-vaccination)

Use of syrup Paracetamol

The frequency of fever occurring within the first 24 hours following vaccination is highest following pentavalent, DPT and IPV. Therefore, it is recommended to give Paracetamol in syrup form after vaccination at 1 ½ months, 2 ½ months and 3 ½ months (first, second and third doses of pentavalent) and at 1 ½ years and 5-6 years (first and second booster doses of DPT).

For the children between 6 weeks to 6 years under the universal immunization programme, syrup paracetamol of strength 125mg/5ml is preferable for uniformity and preventing dosing errors. The recommended doses and frequency of administration of paracetamol syrup (125 mg/5 ml) as per age is as follows:

Age wise dose of Paracetamol syrup (125 mg/5 ml) in infants (recommended dose of Paracetamol: 10-15 mg/kg body weight)		
Age group	**Dose**	**When**
6 weeks - 6 months	2.5 ml	In case of fever* following vaccination and 4-6 hourly thereafter if needed#
6-24 months	5 ml	
2-4 years	7.5 ml	
4-6 years	10 ml	

*Axillary temperature > = 38oC/ 100.4oF or child feels hot to touch
Maximum four doses in 24 hours with a gap of at least four hours between two doses.

Instructions for health workers regarding dispensation of syrup paracetamol

1. COUNT the number of bottles of syrup paracetamol (strength 125mg/5 ml) at the beginning of a session to ensure availability of 10% more bottles than the total number of doses of pentavalent and DPT expected to be administered in the session.
2. DISPENSE one bottle of syrup paracetamol only to children who have been administered pentavalent or DPT in the session.
3. READ bottle label to verify contents (syrup paracetamol, strength 125mg/5 ml) and expiry date.
4. REFER dosage chart and choose volume required per dose as per age of the vaccine recipient.

5. INSTRUCT the care-giver to administer syrup paracetamol to the child only when fever (axillary temperature > = 38oC/ 100.4oF or child feels hot to touch) occurs after vaccination. Do not give if there is no fever.
6. TELL the appropriate dose and SHOW the care giver the markings on the measuring cap of syrup bottle for the dose.
7. USE only the measuring cap supplied with the paracetamol syrup bottle to measure and administer syrup paracetamol to the child.
8. INSTRUCT that not more than 4 doses should be given in 24 hours and a gap of at least 4 hours should be maintained between two doses.
9. DEMONSTRATE shaking the bottle for 10 seconds before use in case suspension is supplied in place of syrup.
10. ADVISE that a doctor should be consulted, if any danger sign is present or fever persists for more than two days even with use of paracetamol.
11. USE the referral protocol for post vaccination fever to determine the need for referral.

Caregivers should be informed and encouraged to practice non-pharmacological methods like breastfeeding before, during and after immunization for relieving pain and crying. Other methods like sponging, skin-to-skin contact and holding the infant are also helpful in reducing pain, fever and crying after immunization.

For details refer to: https://itsu.org.in/aefi/

Annexure 5: Guidelines for Initial Anaphylaxis Management

(Using Injection Adrenaline)

Remember:

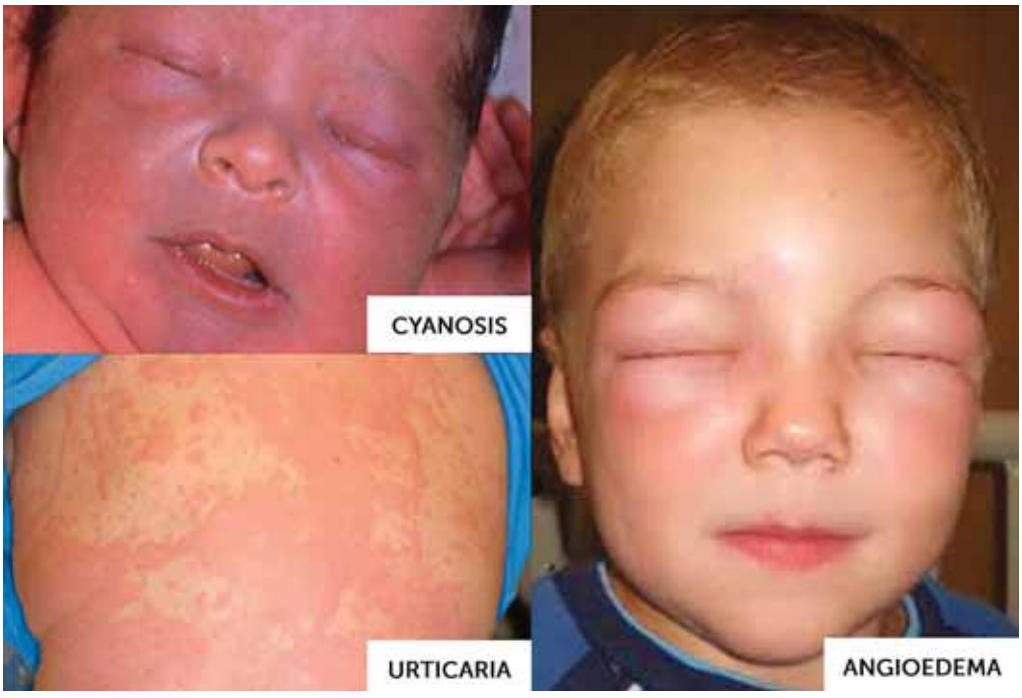
Giving one dose of adrenaline to any suspected case of anaphylaxis intramuscularly is completely safe even if it actually turns out NOT to be a case of anaphylaxis later.

A. Suspecting a Case of Anaphylaxis

A case of anaphylaxis is suspected* if there is early onset (within few minutes to 6 hours of vaccination) and rapid progression of signs and symptoms with involvement of at least one sign/symptom from at least two of the three systems given below:

System	Sign and Symptom
Respiratory	• Swelling in tongue, lip, throat, uvula or larynx • Difficulty in breathing • Stridor (Harsh vibrating sounds during breathing) • Wheezing (breath with whistling or rattling sound in the chest) • Cyanosis (bluish discoloration of arms and legs, tongue, ears, lips etc.) • Grunting (noisy breathing)
Cardiovascular	• Decreased level /loss of consciousness (fainting, dizziness) • Low blood pressure (measured hypotension) • Tachycardia (increased heart rate, palpitation)
Dermatological or mucosal	• Generalized urticaria (raised red skin lesion, rash with itching) • Generalized erythema (redness of skin) • Local or generalized Angioedema- itchy/ painful swelling of subcutaneous tissues such as upper eyelids, lips, tongue, face etc. • Generalized pruritus (itching) with skin rash
Others	• Anxiety, diarrhea, abdominal cramps, nausea, vomiting and sneezing or rhinorrhea.

*Many of the initial signs and symptoms are similar in both mild allergic reactions and severe allergic reactions / anaphylaxis. ANM may administer a single dose of adrenaline injection at the first sign or symptom suggestive of allergy or anaphylaxis



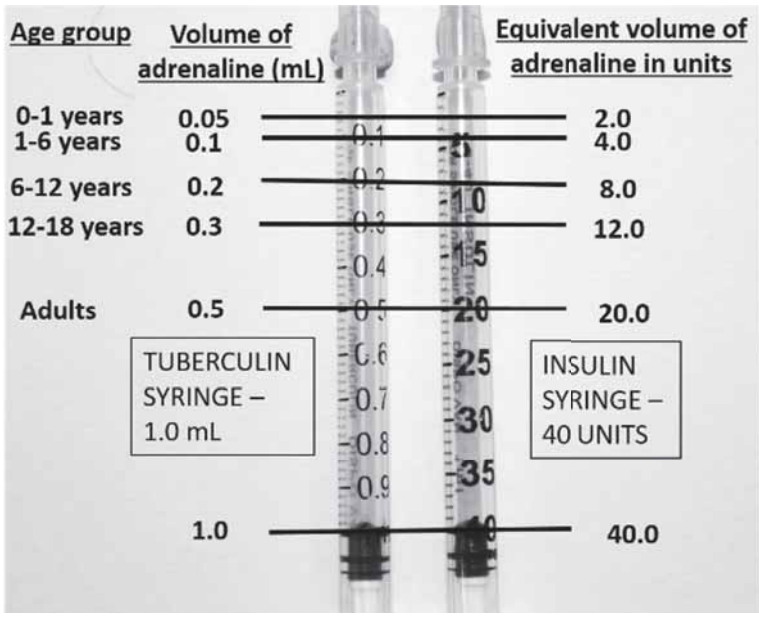
B. Steps to Manage a Case of Suspected Anaphylaxis:

1. Do not panic; reassure patient/parents and care givers.
2. Conscious patient should be kept in a supine position with lower limbs raised higher than head. The unconscious patient should be kept in left lateral position.
3. Immediately administer one dose of injection adrenaline by deep intramuscular route.

C. Steps for Administration of Injection Adrenaline by ANM

1. From the anaphylaxis kit, take one ampoule of adrenaline (1:1000) and check name, dilution and expiry date on label.
2. Take a 1 ml tuberculin / 40 unit insulin syringe and a 24G/25G one inch long needle and use the chart given below to choose and load the required dose of adrenaline as per age and type of syringe supplied.

Age group	Dose in mL (tuberculin syringe)#	Equivalent volume in insulin syringe#
0-1 year	0.05	2
1-6 years	0.1	4
6-12 years	0.2	8
12-18 years	0.3	12
Adults	0.5	20



Based on type of syringe available (tuberculin/insulin), choose relevant volume of adrenaline for administration

1. Use swab to clean the middle 1/3rd of anterolateral aspect of the thigh of the opposite limb to that in which vaccine was given.
2. Give deep intramuscular injection at 90 degree angle to skin in middle 1/3rd of anterolateral aspect of thigh.

D. Transportation, informing MO and documentation

1. Immediately arrange for an ambulance to transport the patient to the nearest health facility well equipped to manage anaphylaxis / health facility (PHC/CHC/District Hospital/ Civil Hospital).
2. As the patient is being transported to health facility, inform medical officer about the case with necessary details (name, age, date, time, site, route and dose of adrenaline administered) for further management at the health facility well equipped to manage anaphylaxis and for follow up.
3. Record the anaphylaxis reaction in the immunization card in block letters.
4. The case details should also be recorded in the AEFI register at the PHC.

Annexure 6: Case Reporting Form (CRF)

CASE REPORTING FORM (CRF)

To be filled by doctor and sent to District Immunization Officer within 24 hours *Mandatory Field

AEFI Case ID: IND (AEFI) / S T / D S T / Y R / N U M (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID: IND (CO-AEFI) / S T / D S T / Y R / N U M (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Reporter and notifier details

Name of doctor reporting / filling this form*: Contact phone number*: E mail*: Place of present posting*: Designation*: Address of present posting:	Reporting Date: __ __ / __ __ / __ __ __ __ (date when this form is prepared) Date case visited and examined / interviewed: __ __ / __ __ / __ __ __ __ (date when the case visited or interviewed)
Notified by (Name)*: Date notified: __ __ / __ __ / __ __ __ __ (date when the case informed to reporting doctor)	Designation of notifier (please circle): ASHA / AWW / Health worker / Government doctor / Private practitioner or hospital / Parent / Community / Media / Others Specify: _____
Address of session site*: Village or Urban area: Block Name: District: State:	**Place of Vaccination*:** Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	**Vaccination in*:** Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19) / Others (specify):_____ **Type of Session Site:** Fixed / outreach / mobile / school / others (specify):_____

Section B : Patient details

Patient Name*																				

Date of Birth * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*	Male / Female

Mother's Name																				
Spouse / Father / Guardian's name*																				

Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.)*

P	**I**	**N**	-							**P**	**H**	**O**	**N**	**E***	-					

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines administered to this case (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer / Brand Name*	Batch / Lot No.*	Mfg. date	Expiry date	Date & Time of vaccine reconstitution / opening vaccine vial	No. of **OTHER** beneficiaries who received vaccine from **SAME** vial in this session

Section D : Details of adverse event(s)

1. Type of Adverse Event: Serious / Severe
2. If serious AEFI specify: Death / Hospitalization / Cluster / Persistent or significant disability / Congenital anomaly or birth defect / Media, community or parental concern

If this is a part of a cluster*: Yes / No / Unknown

If yes number of other cases in the cluster _____ Cluster ID (as generated by SAFE-VAC):

Adverse event(s) - clinical* (TICK AS MANY AS APPLICABLE):

☐ Severe local reaction	☐ Fever	☐ Seizures	☐ Injection site abscess
☐ Sepsis	☐ Encephalopathy	☐ Toxic shock syndrome	☐ Thrombocytopenia
☐ Allergic reaction	☐ Anaphylaxis	☐ Intussusception	☐ Lymphadenitis
☐ Acute Flaccid Paralysis	☐ Hypotonic Hypo-responsive Episode (HHE)	☐ Unexplained Death	☐ Anxiety reaction

Additional for COVID vaccine

☐ Joint pain / swelling of recent onset	☐ Painful single limb swelling	☐ Chest pain / fainting / palpitation
☐ Recent ECG / Echo / angiography changes	☐ Breathlessness / difficulty in breathing / worsening of existing respiratory problem	
☐ Altered sensorium / Loss of consciousness	☐ Acute disseminated encephalomyelitis	☐ Guillain-Barre syndrome
☐ Meningoencephalitis	☐ Mono-neuropathy / Poly-neuropathy	☐ Rashes
☐ Loss of taste / smell	☐ Acute liver injury / Acute Liver Failure	☐ Chilblain-like lesions /vasculitis
☐ Acute kidney injury / Acute Renal Failure / Hematuria / Oliguria / Edema of legs / Hypertension		☐ Lymphadenopathy
☐ Coagulation / bleeding disorder (Thromboembolism, Hemorrhage)		
☐ Worsening of existing disease (Cardiac / Respiratory / Liver / Kidney / Diabetes etc.)		☐ Others (specify).....

Pregnancy related events

☐ Maternal death ☐ Fetal loss (abortion) ☐ Premature delivery ☐ Still birth ☐ Neonatal mortality ☐ Congenital anomaly in newborn

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization (In-patient admission)*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):
If hospitalized, outcome*: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Date & Time of Death*: DD / MM / YYYY (if died) at ___:___AM / PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: Yes / No / Unknown Date of Post mortem: DD / MM / YYYY

Describe AEFI (sequence of events, signs and symptoms after vaccination) *:

Signature and name of Reporting Medical Officer:

Section E: Decision making details

District Immunization Officer to complete and submit in **SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines)** within 24 hours of receiving the above information. SAFE-VAC: **https://safevac.nhp.gov.in**; Co-WIN - SAFE-VAC:

Date report received at District level: __ __ / __ __ / __ __ __ __

Date investigation planned: __ __ / __ __ / __ __ __ __

DIO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure 7: AEFI Register

(to be kept at PHC/cold chain point/sector or block PHC/facility conducting vaccination) (to be filled by ANMs once a week)

Date of entry	Name of Facility/ Centre	Name of the patient	Mother's / Father's name (with mobile no.)	Date of birth	Sex	Date & time of vaccination	Name of vaccines given	Manufacturer name with batch number of vaccines given	Date and time of onset of symptom(s)	AEFI sign / symptom / diagnosis	Type of AEFI (minor / serious/ Severe)	Reporting of serious / severe case using CRF (if yes – mention date / otherwise mention No)

Please note:

- All AEFI recorded in this register during the month are to be entered in HMIS report at the end of the month.
- Medical Officer in-charge to verify the weekly AEFI (minor, severe and serious) entries and sign.
- If no AEFI (minor, severe and serious) is recorded in a week, then the Medical Officer in-charge should certify for 'No case reported' and sign.

Assessment of AEFIs recorded at the Planning unit level

(Format to be shared in the first week of every month to DIO)

To be filled by MO in charge

Month **Year**

Name of the BLOCK PHC/CHC/Facility along with MO in charge: Phone Number:	Block Name: District:	Date:

Following table need to be filled up after reviewing AEFI register of respective month. Tabulate the data for all (minor/severe/serious) AEFIs listed in respective month.

Name of Planning unit /Facility/ Centre	Minor AEFI			Serious/Severe AEFI				Any other (specify)
	Fever < 39° C	Injection site reaction (pain/ redness and swelling)	Irritability, malaise, fatigue, loss of appetite	Fever >39° C	Allergic reaction	Abscess	Seizures	
Total								

Any Aggregation or Clustering (Tick as appropriate)	Possible reason	Action proposed
A) Antigen wise and Batch wise - If antigen wise, does it exceed expected reaction rate. Refer Table No. 1 (Yes /No)		
B) Sub-centre wise/Vaccinator wise		
C) Any other (e.g. unusual event)		

Name of in-charge Medical officer: Signature with date:

Annexure 8: Case Investigation Form (CIF)

CASE INVESTIGATION FORM (CIF)

(To be submitted in SAFE-VAC / Co-WIN – SAFE-VAC within 21 days of notification) *Mandatory Field

AEFI Case ID : IND (AEFI) / S T / D S T / Y R / N U M (from SAFE-VAC, for all vaccines except COVID-19 vaccines)

AEFI Case ID : IND (CO-AEFI) / S T / D S T / Y R / N U M (from Co-WIN - SAFE-VAC, for COVID-19 vaccines)

Section A: Basic details (Please refer to CRF of this case for personal details of patient)

Name of the Lead Investigator*:	Designation*:
Contact phone number* : E mail*:	Date of case visit and investigation: __ __ / __ __ / __ __ __ __ (date when the case was contacted/investigated)

Address of session site*: Village or Urban area: Block Name: District: State:	**Place of Vaccination*:** Govt Health Facility / Outreach / Private Health Facility / Others (specify): _____ Source of vaccine: Government supply / Privately purchased / Others (specify): _____
Date of Vaccination*: __ __ / __ __ / __ __ __ __ Time of Vaccination: __ __ : __ __ AM/PM	**Vaccination in*:** Routine Immunization / Campaign (MI, Pulse Polio, MR, JE, COVID 19 / Others (specify):_____ **Type of Session Site:** Fixed / outreach / mobile / others (specify):_____

Section B : Patient details

Patient Name*:				
Date of Birth of patient * DD/MM/YYYY	Age: _____ years ___ Months ___ days	Sex*:	Male	Female
Mother's Name:				
Spouse/Father's Name:				
Complete Address* with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No. etc.):*				
PIN: Phone:				

For women in reproductive age group:

1. Status of pregnancy at the time of vaccination: Yes / No / Don't know
2. If Yes, duration of pregnancy at the time of vaccination: 1-3 months / 4-6 months / 7-9 months
3. Lactating at the time of vaccination: Yes / No / Don't know

Section C : Details of vaccine(s) and diluent(s) administered to the AEFI case during this session (to be filled by MO incharge or DIO of area where vaccination took place)

Name of vaccines received (write vaccine & diluent details in separate rows)*	Dose no. (birth / zero / 1st / 2nd / 3rd / booster 1 / booster 2 / campaign)*	Name of Manufacturer/Brand name*	Batch / Lot No.	Expiry date*	Mfg. date	Date & Time of opening vaccine vial / vaccine reconstitution	No. of **OTHER** beneficiaries who received vaccine from **SAME** vial in this session

Date & Time of first symptom*: DD / MM / YYYY at ___:___AM/ PM	Hospitalization*: Yes / No
Name and address of hospital:	
Date & Time of hospitalization*: DD / MM / YYYY at ___:___AM / PM	Hospital Reg. No. (OPD/Admission/Bed Head Ticket):

Date & time of death*: DD / MM / YYYY (if died) at ___:___AM/ PM Place of death: Home / Hospital / On the way to hospital / Others	Post mortem done: YES / NO / Unknown If done, date of post mortem: DD / MM / YYYY
If hospitalized, outcome *: Discharged / Still Hospitalized / Left Against Medical Advice (LAMA) / Absconded / Referred / Death / Brought dead	
Current status of patient*: Recovered completely / recovered with sequalae / still under treatment / death / unknown	
Describe AEFI (sequence of events, signs and symptoms after vaccination)*:	

Section D Relevant patient information prior to immunization:

Criteria	Finding	Provide details here if "yes" marked to any question@
Any past history of similar reaction event (without vaccination)?	Yes / No / Unknown	
Any adverse event after previous vaccination(s)	Yes / No / Unknown	
Any history of allergies for drugs, vaccine, food or other products?	Yes / No / Unknown	
Any concomitant medication at the time of vaccination, if any (If yes, name the drug, indication, doses, treatment dates/duration)?	Yes / No / Unknown	
Any pre-existing illness / comorbidity / congenital disorder?	Yes / No / Unknown	
Any pre-existing acute illness 30 days prior to vaccination?	Yes / No / Unknown	
Any history of hospitalization 30 days prior to vaccination (mention reason)?	Yes / No / Unknown	
Family history of any disease (relevant to AEFI) or allergy	Yes / No / Unknown	
Has the patient tested COVID-19 positive prior to this vaccination? If yes- Type of test (RTPCR/Rapid test/CBNAAT/TRUNAAT): Date of the test:	Yes / No / Unknown	
Has the patient been in contact with a COVID-19 positive individual within 30 days prior to vaccination?	Yes / No / Unknown	
Has the patient developed symptoms compatible with COVID-19 in the past?	Yes / No / Unknown	

If patient is an infant or baby born to pregnant woman vaccinated during pregnancy, give birth details:	Remarks
1. Birth Weight:	
2. Duration of pregnancy ☐ Full term ☐ Pre-mature ☐ Postdated ☐ Unknown	
3. Place of birth ☐ Home delivery ☐ Institutional ☐ Unknown	
4. Delivery procedure ☐ Normal ☐ Caesarian ☐ Assisted with forceps/vacuum ☐ Unknown	
5. Any antenatal / postnatal complications: Yes / No / Unknown; if yes please specify _____	

Section E Detailed clinical assessment, investigation, diagnosis and treatment of reported AEFI case@

@Instructions:

- *In case of Unexplained Death in infant* - please fill Verbal Autopsy form as per the guidelines
- *If patient has taken medical care* - attach copies of all available documents (including OPD prescriptions, prescription for concomitant medication, case sheet, discharge summary, laboratory/investigation reports and post mortem reports, if available) and then complete additional information NOT AVAILABLE in the attached documents
- *If patient has not taken any medical care* - obtain history, examine the patient and write down your findings below (add additional sheets as required)

Source of information (✓ *all that* apply): ☐ AEFI Case Reporting Form ☐ Examination by the investigator ☐ Medical case records ☐ AEFI Verbal autopsy form ☐ Interview with patient / caregiver ☐ Telephonic enquiry with patient / caregiver ☐ Interview with treating physician ☐ Other_____

Date of examination: Signs and Symptoms:

Consciousness: Alert / Drowsy / Unconscious / Other (specify and describe) .....

Vitals: Pulse ..... Temperature ..... Respiratory rate ..... BP ..... Weight .....

Skin: Rash/Cyanosis/Petechiae/Pallor/Jaundice/Others (specify and describe) .....

COVID-19 test status after vaccination (if conducted, with date and type of test)

Test conducted: Y / N If Y, date of test: Test result: Positive / Negative / Not known Type of test:

Has anyone in the family of the patient tested COVID 19 positive after vaccination? Y/N. If Y, then date of test:

Has the patient developed symptoms compatible with COVID 19 infection after vaccination? Y/N. If Y, then date of test:

Systemic examination findings (mention the important positive and negative findings):

Treatment provided:

Provisional / Final diagnosis (as per the treating doctor and/or the Investigation team [encircle one] , if no medical care received):

Section F Investigation at vaccination site

Details of vaccines provided on vaccination day at the site linked to AEFI

Number immunized for each vaccine at session site. Attach record if available.													
	Vaccine name												
	No of doses administered												
	Number of vaccine vials used												

1. Sequence of patient -
   a. At session site on day of vaccination:
   ☐ Within the first half beneficiaries at the session site ☐ Within the last half beneficiaries the session site ☐ Unknown
   b. For a multi dose vaccine vial (since the vial has been opened):
   ☐ Within the first half beneficiaries of the vaccine vial ☐ Within the last half beneficiaries of the vaccine vial ☐ Unknown
   If required, sequence of vaccination of all subjects (affected and not affected) should be established and mentioned on a separate sheet

2.	Multidose vials administered to the case	No. of beneficiaries vaccinated from each vial on session day	No. of beneficiaries vaccinated from same vial since opening or reconstitution	No. of times each vial was issued to sessions before being issued to this session
a.				
b.				
c.				
d.				
e.				

3.	**Is this case a part of a cluster?**	Yes / No / Unknown
	A If yes, how many other cases have been detected in the cluster?	
	B Did all the cases in the cluster receive vaccine from the same vial?	Yes / No / Unknown
	C If no, Number of vials used in the cluster	

4. If similar events have been reported from other session sites, comments:

Immunization practices <u>at the place (s) where concerned vaccine was used</u> (based on observations and assessment)				
5. **Syringes and Needles Used:**				
• Were/Are AD syringes used for immunization? • If no specify the type of syringes:				Yes / No / Unknown
Specific key findings/additional observations and comments:				
6. **Reconstitution: (complete only if applicable, ✓ NA if not applicable)**				
• Reconstitution procedure (✓)	Status			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA	
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA	
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA	
• Were/Are the diluents used same as recommended by the manufacturer?	Yes	No	NA	
7. **Vaccine handling and vaccination** (examine the available used vaccine vials and observe an immunization session, if needed)				
• Noncompliance to recommendations for use of this vaccine (e.g. any contraindication ignored?)				Yes / No / Unknown
• Wrong selection of the beneficiary(ies) (e.g. NOT age appropriate for the vaccine)				Yes / No / Unknown
• Unsterile condition of the vaccine (ingredients) or diluent administered (sterile/unsterile)				Yes / No / Unknown
• Abnormal vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances, etc.)				Yes / No / Unknown
• Error in vaccine reconstitution/preparation by the vaccinator (e.g., wrong product, wrong diluent, improper mixing, improper syringe filling etc.)				Yes / No / Unknown
• Date and time of opening the vial clearly NOT mentioned on the vials being used in the session under observation				Yes / No / Unknown
• Error in vaccine handling (break in cold chain during transport, storage and/or immunization session etc.)				Yes / No / Unknown
• Error in vaccine administration (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?				Yes / No / Unknown
Specific key findings/additional observations and comments:				

Section G **Cold Chain and Transport (Answer the following based on observations and assessment)**	
Last vaccine storage point:	
• The temperature of the ILR/vaccine storage refrigerator monitored (thermometer and documentation)	Yes / No
○ If, 'yes', any deviation outside of 2- 8°C after the concerned vaccine vial was received at cold chain point	Yes / No
○ If, 'yes' attach relevant monitoring documents separately	
• Correct procedure of storing vaccines, diluents and syringes followed	Yes / No / Unknown
• Any other item (other than vaccines and diluents) available in the refrigerator or freezer	Yes / No / Unknown
• Partially used reconstituted vaccines available in the refrigerator	Yes / No / Unknown
• Unusable vaccines (expired, no label, VVM stage 3 & 4, frozen) available in the refrigerator	Yes / No / Unknown
• Unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) available in the store/refrigerator	Yes / No / Unknown
Specific key findings / additional observations and comments:	
Vaccine Transportation:	
• Type of vaccine carrier used	4-icepacks / 2-icepacks / other
• Conditioned ice-pack used in the vaccine carrier	Yes / No / Unknown
• Vaccine carrier sent to the session site on the same day of vaccination	Yes / No / Unknown
• Vaccination carrier returned from the session site on the same day of vaccination	Yes / No / Unknown
• All empty/partially used/unused vaccine vials (and diluents) return to cold chain point on the same day of vaccination	Yes / No / Unknown
• Comment on vaccine handling (any error, e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	
Specific key findings/additional observations and comments:	

Section H	**Community Investigation (Please visit locality and interview parents/ others)**
Any similar events reported recently in the locality? Yes / No/ Unknown If Yes, Describe:	
If Yes, How many events / episodes and the category of people affected (children, adults, any specific locality/area)?	
Of those affected, how many are • Vaccinated:_____ • Not Vaccinated:_____ • Unknown:_____	
Other findings beyond vaccine or vaccination:	

Section I	**District AEFI Committee Review**		
a)	*What was the provisional diagnosis of the case concluded by the District AEFI committee?*		
b)	*Please describe the events, clinical and epidemiological findings in support of provisional diagnosis.*		
c)	*Any biological product sent (CSF, Blood, urine, tissue extracts) for testing? Note: for AEFI resulting within 28 days following JE vaccine, send sample of CSF, Serum to nearest NIV lab in Pune or Gorakhpur or Mumbai*		
d)	Did the district AEFI committee recommend sending vaccine samples for quality testing?	Yes	No
e)	Was local drug inspector involved in collecting additional samples?		
f)	Specify any other relevant investigation done and attach reports.		

Details of Vaccine/ Diluent samples sent to CDL Kasauli

Vaccine/Diluent Name	Site of collection	Used Vial/Amp. Quantity	Batch no, Lot no, date of expiry	Date Sent	Unused Vial / Amp. Quantity	Batch no, Lot no, date of expiry	Date Sent

Details of Syringe/ Needle samples sent to CDL Kolkata

Type of Syringes	Quantity	Site of collection	Batch no, Lot no, date of expiry	Date Sent	Type of Needles	Quantity	Batch no, Lot no, date of expiry	Date Sent

Based on the investigation, answer the following: *(Please provide explanation in the remark column for any 'yes')*

A	Could the vaccine given to this patient have quality defect or is substandard or falsified?	Yes / No / Unable to assess	Remark
B	In this case, was there an error in prescribing or non-adherence to recommendations for use of this vaccine? (e.g. use beyond the expiry date, wrong recipient etc.)	Yes / No / Unable to assess	Remark
C	In this case, was the vaccine (ingredients) or diluent administered in an unsterile manner?	Yes / No / Unable to assess	Remark
D	In this case, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	Yes / No / Unable to assess	Remark
E	When this case was vaccinated, was there an error in vaccine reconstitution / preparation by the vaccinator (e.g., wrong product,	Yes / No / Unable to assess	Remark

	wrong diluent, improper mixing, improper syringe filling etc.?		
F	In this case, was there an error in vaccine handling? (e.g. Break in cold chain during transport, storage and/or immunization session etc.)?	Yes / No / Unable to assess	Remark
G	In this case, was the vaccine was administered incorrectly (e.g. wrong dose, site or route of administration, wrong needle size, not following good injection practice etc.)?	Yes / No / Unable to assess	Remark
H	In this case, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety etc.)?	Yes / No / Unable to assess	Remark

Section J: Attached copies of reports / documents etc. with this Case Investigation Form:

S. No.	List of document copies received (check appropriate box)	Available and submitted with CIF	Will be available, pending for submission	Not applicable	Applicable, but not available	Remarks (if any)
1.	Case Reporting Form (CRF)					
2.	Hospital patient treatment records / hospital discharge summary *(in case of hospitalized cases)* / doctor's OPD prescription / day care treatment record / OPD treatment record)					
3.	Doctor's prescription / treatment record for past / preexisting illness					
4.	Any clinical laboratory test report (Pathology / Microbiology / Hematology / Blood / CSF / Urine / AFP / any radiology imaging report / EEG report, etc.)					
5.	Post Mortem Report – preliminary *(in case of death)*					
6.	Post Mortem Report – final *(in case of death)*					
7.	Verbal Autopsy Form (in case of unexplained death/ not hospitalized)					
8.	Laboratory result of vaccine (if sent for testing)					
9.	Laboratory result of syringes/other drugs (if sent for testing)					
10.	Any other document relevant to case					

District AEFI Committee members

Name	Designation	Phone Number	Signature
1.			
2.			
3.			
4.			
5.			
6.			
7.			

Section K: DIO/ RCHO/ District Nodal Person *(Officer forwarding this report)*

DIO/ DRCHO/ District Nodal Person *(Officer forwarding this report)*

Name ..... Designation..... Mobile No*: .....

Email id*: ..... Signature..... Date/ Seal: .....

Complete Office address (with Pin code) .....

.....

District Immunization Officer to complete and submit in **SAFE-VAC / Co-WIN SAFE-VAC (for COVID-19 vaccines)** within 21 days of receiving the above information. SAFE-VAC: **https://safevac.nhp.gov.in; Co-WIN - SAFE-VAC: https://www.cowin.gov.in/**

For any support or help, write to: aefiindia@gmail.com; safevac.chi@gmail.com

Annexure 9: Case Notification Form (CNF)

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.**

Annexure 10: Verbal Autopsy Form for Children

Questionnaire for interviewing family of reported AEFI death of a child aged 0-18 years

To be filled in every death reported as an AEFI irrespective of whether post-mortem has been conducted or not

I would like to ask you some questions concerning signs and symptoms that the child had/showed when s/he was ill prior to and at the time of event, any previously known medical conditions; injuries and accidents that the child suffered. Some of these questions may not appear to be directly related to the event. Please bear with me and answer all the questions. They will help us to get a clear picture of what led to the child's death.

Date and time of interview: Place of Interview:

Section 1. Basic Details

A) Patient identifiers

EPID No. (SAFEVAC) -	
State:	District:
Block:	PHC:
Name of the Child:	
Sex: Male/Female	
Date of Birth:	Age (in days/months/years):

Name of Head of the Household:
Complete Address:

Phone No.:

B) Details of respondents:

Sr. No.	Name of respondent	Age/ Sex	Relation with deceased
1			
2			
3			
4			

Name of the main respondent:

Education:

Did the respondent live with the deceased during the events that led to death? (Yes/No)

Date & Time of death:

Place at which death occurred (encircle one) - Home/Government facility/Private facility/others (please specify):_____

C) Family History

Number of people staying in the house and relation to the child /person:

Number of siblings:

Details of siblings:

S. No.	Name of sibling	Age & sex	Birth order	Health status of sibling
1.				
2.				
3.				
4.				

Consanguinity Yes/No (If yes, specify_____)

Recent illness in family Yes/No (If yes, specify_____)

Occupation of father:

Occupation of mother:

History of similar illness/death of any child in family – Yes/No. If yes, give details:

Presence of adverse family circumstances - Yes/No

If yes, encircle - family relationships/ economic/ behavioral/ addictions/others-

Give details -

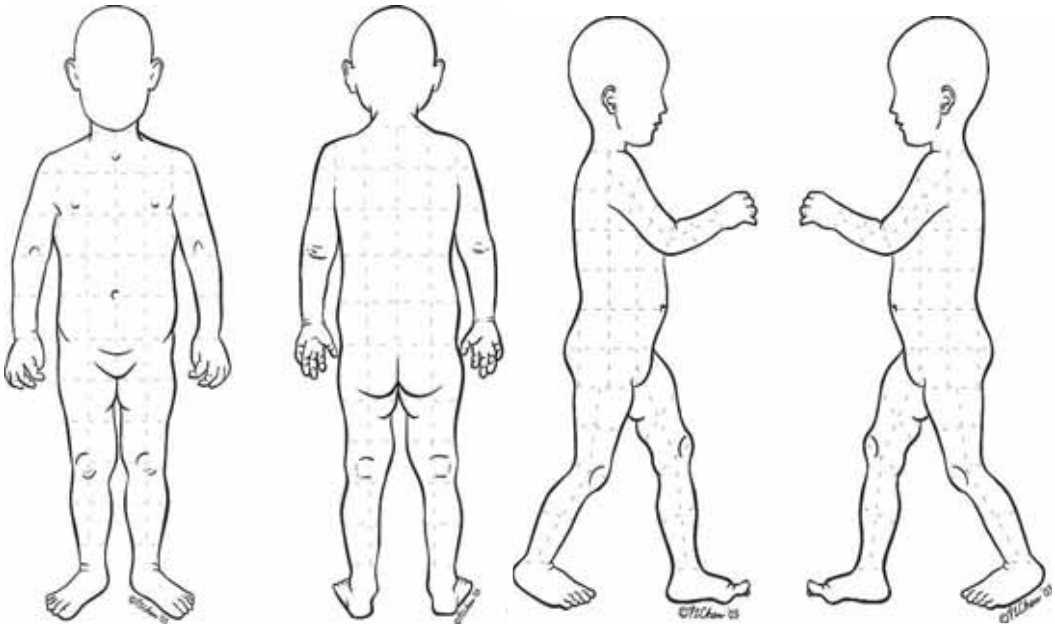
D) Details of current vaccination:

Date: Time: Place:

Who administered the vaccine(s): ANM…LHV…..PHN….Pharmacist……Doctor……others…..specify

Vaccine name	Route (injectable or oral)	Site (verify site from mother)
Vaccine 1		
Vaccine 2		
Vaccine 3		
Vaccine 4		
Vaccine 5		

Fig-1: Drawing of front, back, left side and right side of infant to mark injection sites with respective vaccines and location of swelling at or near injection site. (source: Brighton Collaboration definitions)



E) Past history of the child:

Check immunization card (if available) or collect information from AWW/ANM or PHC and specify which vaccines were received and when -

Reactions to previous vaccines Yes/No. If yes, specify_____

History of Previous allergy Yes/No. If yes, specify_____

Seizures/breath-holding spells/cyanosis Yes/No. If yes, specify_____

Pre-existing illness Yes/No. If yes, specify_____

History of hospitalization in last 30 days with cause Yes/No. If yes, specify_____

History of medication intake on long term/during last week Yes/No (If yes, note down details from previous medical records or attach copies

F) Nutritional status:

Weight (in kgs): _____Date recorded - __/__/____(Check vaccination card/ medical records)

If weight is not available, ask whether the child looked weaker/smaller as compared to babies of similar age - Yes /No

Section 2. For children (0- 5 years). For older children, skip to section 3

A) Birth details (check records if available):

Birth weight: kgs.

Child's size (if weight is unknown at birth)- Small/average/larger than average/unknown

Place of delivery - Type of delivery - Normal/caesarean/forceps

Did pregnancy result in single child/twins/multiple births?

Was the child born premature? Yes/No. (If yes, please specify details_____

Did s/he have any malformation/s at birth? Yes/No (If yes, please specify details-

Were there any complications during pregnancy/at birth? Yes/No. If yes, give details-_____

Was the child hospitalized in the first month of life? Yes/No (If yes, give details_____

B) Feeding history:

Breast-fed Yes/No

Other foods Yes/No (If yes, specify_____)

What foods and liquids were the child fed in **the last 24 hours (include last feed)?**

Type of feed	Y/N	Frequency in last 24 hours	Time of the last feed (hours before death)	Mode of feeding (breastfeed/Bottle/katori spoon/glass)
Breast milk				
Animal milk				
Water				
Other liquids				
Semi solids/ Solids				

C) Developmental status:

Appropriate for age/delayed: If delayed, give details:

D) Events observed after this vaccination

What adverse event did the child have after this vaccination? (See the options below)

Condition	**Unknown**	**No**	**Yes**	**Specify time & order of event after vaccination**
Fever				
Diarrhea				
Excessive sweating				
Stool changes (blood/mucus)				

Lethargy or sleeping more than usual				
Fast/Difficulty in breathing				
Fussiness or excessive crying				
Apnea (stopped breathing)				
Poor feeding				
Cyanosis (turned blue/gray)				
Vomiting				
Seizure/s or convulsion/s				
Skin rash/flushing				
Choking				
Any other (please specify)				

Describe details in your own words -

E) In case of death at home:

S. no.	Question	Last known alive	When put to bed last	When found dead
1.	Where was the child placed last? (crib, bed, floor, jholi, etc.)			
2.	In which position? (Sitting/ on back/on side/on stomach/ unknown)			
3.	What was the child wearing?			
4.	How was the face positioned? (Face down on surface/face up/face side)			
5.	What was the temperature inside the child's room? (Hot/cold/normal/other, please specify)			
6.	Was anyone sleeping with/ near the child?			
7.	Which of the following items were found/ placed near the child? (like toys/pillows/ polythene bags/			

	blankets/ sheet/ others, please specify _____ _____)			
8.	Was any electrical /traditional equipment used to heat the room/area where the event occurred? (Specify)			

When the infant was found, was s/he breathing/not breathing?
If not breathing, did you witness the infant stop breathing? (Yes/No)
What has led you to check on the infant?

Describe the infant's appearance when found:

Appearance	Unknown	No	Yes	Describe and specify location
Discoloration around face/nose/mouth				
Secretions (foam, froth, blood)				
Skin discoloration				
Pressure marks (pale areas/blanching)				
Rash or petechiae (small, red blood spots on skin, membranes, or eyes)				
Marks on body (scratches or bruises)				
Other				

What did the infant feel like on touch when found? _____
(Sweaty/warm to touch/cool to touch/limp, flexible/rigid, stiff/unknown /others, please specify)

Did anyone try to revive the child? Yes/No
(If yes, give details_____)

Section 3: Details of treatment received for this adverse event. This section should be mandatorily filled in all cases.

1. Did the child receive any treatment for this event – Yes/No. If yes,
   a) Where *(describe in chronological order)* - Home/ Traditional healer /Government clinic/Government hospital/private clinic /private hospital/chemist store/Any other place or facility (specify)- _____

   b) Give details of medicines administered-
   (Ask for prescriptions/partially used blister packs or bottles to verify, where possible.)

   c) Was the child referred to any higher center? If yes, to which facility and when?

2. In the month before the event, did the child have any contact with any health services? Yes/ No. If yes, give details:_____

3. Did a healthcare worker tell you the cause of the current event? Yes/No. If yes, what was the cause told by the health worker?

4. Are prescription/discharge notes available? Yes/No. If yes, what is the provisional and final medical diagnosis made by the treating unit (attach copy of all available medical records)

5. Copy of Death Certificate available? Yes/No. If yes, what is the cause of death written in the death certificate?

Section 4: Respondent/ Witness interview

Did the respondent witness the events that led to death - Yes/No.

If not, identify the person who witnessed the events prior to death, and record the following:

Witness name and relation to the child:

Are you the usual caregiver? (Yes/No)

How was the injection site? Encircle - Normal/red or blue discoloration/swelling/any other, please specify_____.

Tell me what happened (Record verbatim: narrative of the witness/ respondent in his/her own words):

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Any other comments /observations about circumstances of the event?

_____
_____

If any bystander/neighbour or any other person has information regarding the event or circumstances around the event, give details of the person and the information –

_____
_____
_____

_____
_____
_____
_____

Section 5: Interviewer's observations (Case Summary) (To be filled in after completing the interview. Emphasis should be placed on establishing exact chronology of event from point of vaccination to occurrence of event)

_____
_____
_____

_____
_____
_____
_____
_____

Note: If any of the details in sections 4 and 5 have been recorded in local language, please attach a translation in English.

Section 6: Final diagnosis:_____

Attach copies of all available documents (including case sheets, discharge summary, laboratory reports and postmortem reports).

Signature and Date	**Signature and Date**	**Signature and Date**
Name of interviewer:	**Name of interviewer:**	**Name of interviewer:**
Designation:	**Designation:**	**Designation:**
Contact no.:	**Contact no.:**	**Contact no.:**
Address:	**Address:**	**Address:**
Email Address:	**Email Address:**	**Email Address:**

Annexure 11: Verbal Autopsy Form for Adults

Questionnaire for interviewing family of reported AEFI death of an adult >18 years of age

To be filled in every death reported as an AEFI irrespective of whether post-mortem has been conducted or not

I would like to ask you some questions concerning signs and symptoms that the deceased person had/showed prior to and/or at the time of death, previously known medical conditions the deceased person had, and injuries and accidents that the deceased person suffered. Some of these questions may not appear to be directly related to the death. Please bear with me and answer all the questions. They will help us to get a clear picture of all possible conditions that the deceased person had.

Date and time of interview: Place of Interview:

Section 1. Basic details:

A) Patient identifiers

Name of the deceased person:
Sex (Male/Female/Other):
Age (years): Date of birth:
Educational status of deceased:
Occupation of the deceased:
Marital status of deceased:
State: District: Town: Block: Village:
Complete address:
Pin code:
Name of the head of the Household:
EPID NO..... / ..... / .....

B) Details of respondent

S. No.	Name of respondent	Age/ Sex	Relation with deceased
1			
2			
3			
4			
5			
6			

Main respondent's name: Education:

Contact number:

Did the respondent live with the deceased during the events that led to death? (Yes/No)

Date and time of death: _____

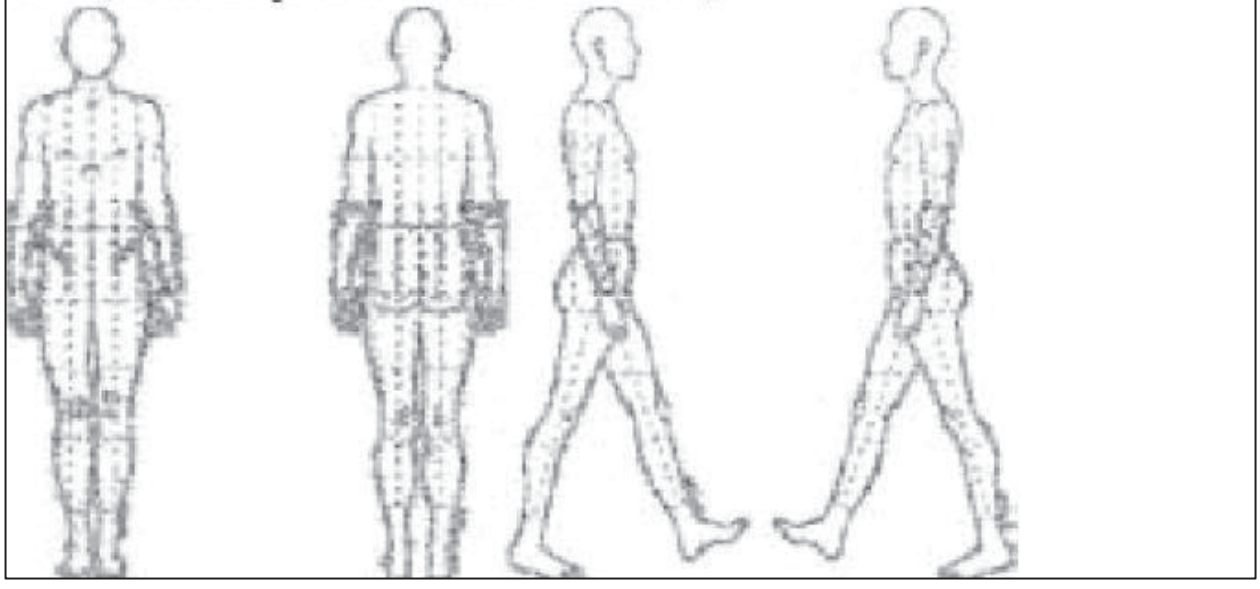
Place of death: Home/govt facility/private facility/others specify_____

C) Details of current vaccination:

Date: Time: Place:

Vaccine name/Brand name	Route (IM/ID/SC)	Site (Verify site from the respondent)

Fig.1. Drawing of front, back, left side and right side of adult to mark injection sites with respective vaccines, location of swelling at or near injection site and position at time of death. (Source: Brighton collaborations definitions)



- Who administered the vaccine(s): ANM/LHV/PHN/Pharmacist/Doctor/Others specify _____

D) Past history of the deceased person

- Previous immunization received:

(Collect immunization card if available and check details)

- Reactions to previous vaccines: Yes/No (If yes, specify) _____
- Pre-existing illness: Yes/No (If yes, specify) _____
- History of Hospitalization in the last 30 days with cause____: Yes/No (If yes, specify)

  _____

  _____
- History of any medication: Yes/No (If yes, specify)

  _____
- Weight of the deceased person (in kgs):

Section 2: Respondent's account of illness/events leading to death

- Could you tell me the events that led to his/her death?

  _____
  _____
  _____
  _____
  _____

- Cause(s)/ circumstances of death according to the respondent?

  _____
  _____
  _____
  _____
  _____

Section 3: History of previously known medical conditions:

Please tell me if the deceased suffered from any of the following illnesses in the past:

1. High Blood Pressure: Yes/No/Don't Know
2. Diabetes: Yes/No/Don't Know
3. Asthma: Yes/No/Don't Know
4. Chronic Lung disease: Yes/No/Don't Know
5. Stroke: Yes/No/Don't Know
6. Cancer: Yes/No/Don't Know (If Yes, specify) _____
7. Coronary artery disease: Yes/No/Don't Know
8. Epilepsy/Convulsions: Yes/No/Don't Know
9. Allergy/Atopy (to specify): Yes/No/Don't Know
10. Suicidal thoughts/Any other psychiatric illness: Yes/No/ Don't know (If Yes, specify)_____
11. Tuberculosis: Yes/No/Don't Know
12. COVID-19: Yes/No/Don't Know
13. HIV/AIDS: Yes/No/Don't Know
14. Malnutrition: Yes/No/Don't Know
15. History of early sudden death in family member's especially first degree relatives: Yes/No/Don't Know
16. Any other medically diagnosed illness: Yes/No/Don't Know (If Yes, specify)_____

Section 4: History of injuries/accidents:

1. Did s/he suffer from any injury or accident that led to his/her death? Yes/No/Don't know
2. If yes, what kind of injury or accident did the deceased suffer? (encircle one) - Road traffic accident/ Fall/ Drowning/ Poisoning/Burns/Violence or Assault/Other (Specify_____)/don't know
3. Was the injury or accident intentionally inflicted by someone else? Yes/No/Don't know
4. Do you think s/he has committed suicide? Yes/No/Don't know
5. Did s/he suffer from any animal/snake/scorpion or insect bite that led to his/her death? Yes/No/Don't know (If yes, specify)_____
6. Did s/he suffer from lightning strike? Yes/No/don't know

If the patient is a woman, complete Section 5. If patient is not a woman, go directly to Section 7.

Section 5:

1. Did she have an ulcer or swelling in the breast? Yes/No/don't know. (If yes, for how long?) _____
2. Did she have excessive vaginal bleeding during menstrual periods? Yes/No/don't know. (If yes, for how long?) _____
3. Did she have menstrual bleeding in between menstrual periods? Yes/No/don't know. (If yes, for how long?) _____
4. Did she have abnormal vaginal discharge? Yes/No/don't know. (If yes, for how long?) _____
5. Did she have vaginal bleeding after cessation of menstruation? Yes/No/don't know. (If yes, for how long?) _____
6. Did she have an operation to remove her uterus shortly before death? Yes/No/Don't know

Section 6: (If response to Q19 is No/Don't know, skip to Q26)

1. Was she pregnant at the time of death? Yes/No/don't know
   If yes for how long was she pregnant? (Weeks/Months/don't know)
2. How many pregnancies had she had including this one? _____
3. During the last 3 months of pregnancy did she suffer from any of the following illnesses?
   a. Vaginal bleeding? Yes/No/don't know
   b. Foul smelling vaginal discharge? Yes/No/don't know
   c. Puffiness of face? Yes/No/don't know
   d. Headache? Yes/No/don't know
   e. Blurred vision? Yes/No/don't know
   f. Convulsion? Yes/No/don't know
   g. Febrile illness? Yes/No/don't know
   h. Severe abdominal pain that was not labor pain? Yes/No/don't know
   i. Pallor and shortness of breath? Yes/No/don't know

4. Did she suffer from any other illness _____? Yes/No/don't know
5. Did she die during labor, but undelivered? Yes/No/don't know
6. Did she give birth recently? Yes/No/don't know
7. How many days after giving birth to her child did she die? _____in days
8. Was there excessive bleeding on the day labor started? Yes/No/don't know
9. Was there excessive bleeding during labor before delivering the baby? Yes/No/don't know
10. Was there excessive bleeding after delivering the baby? Yes/No/don't know
11. Did she have difficulty in delivering the placenta? Yes/No/don't know
12. Was she in labor for unusually long (more than 24 hours)? Yes/No/don't know
13. Was it a normal vaginal delivery? Yes/No/don't know
    If No, what type of delivery was it? Forceps/Vacuum/LSCS/other please specify_____
14. Did she have foul smelling vaginal discharge? Yes/No/don't know
15. Where did she give birth? Home/Hospital/Other health facility _____
16. Who conducted the delivery? Doctor/Nurse or Mid Wife/ Traditional birth attendant/relative/Mother/ by herself/other/don't know
17. What was the birth weight of the baby? _____ kg/grams
    If birth weight is not known, what was size of the baby (ask to show photo if available)? Average/bigger than average/ smaller than average/do not know
18. Was the baby's body soft, pulpy and discolored and the skin peeling away? Yes/No/don't know
19. Did she experience an abortion recently? Yes/No/don't know
20. Did she die during the abortion? Yes/No/don't know
21. How many days before death, did she have an abortion? _____
22. How many months pregnant was she when she had the abortion? _____
23. Did she have heavy bleeding during the abortion? Yes/No/don't know
24. Was the abortion spontaneous or induced? Yes/No/don't know
25. Did she take medicine or treatment to induce the abortion? Yes/No/don't know
26. Did she have any altered sensorium? Yes/No/don't know
27. Did she have weakness in any limb? (Mono/hemi/quadriparesis/other)
28. Did she have any history of neck stiffness? Yes/No/don't know
29. Did she have jaundice during pregnancy? Yes/No/don't know
30. Did she have any history on single limb swelling? Yes/No/don't know

Section 7: Symptoms and signs noted during the final illness with respect to systems:

General questions:

1. For how long was s/he ill before s/he died? _____
2. Did s/he have fever? Yes/No/don't know (If yes, for how long? Specify)_____

3. Was the fever continuous or intermittent? (Continuous/Intermittent/ don't know)
4. Did s/he have fever only at night? Yes/No/don't know
5. Did s/he have chills and rigor? Yes/No/don't know

A. Questions pertaining to RESPIRATORY system: (If response to Q1 is No/Don't know, skip to Q5)

1. Did s/he have a cough? Yes/No/don't know (If yes, for how long specify)_____
2. Was the cough severe? Yes/No/don't know
3. Was the cough productive with sputum? Yes/No/don't know
4. Did s/he cough out blood? Yes/No/don't know
5. Did s/he have night sweats? Yes/No/don't know
6. Did s/he have breathlessness? Yes/No/don't know (If yes, for how long_____)
7. Was s/he unable to carry out daily activities due to breathlessness? Yes/No/don't know
8. Was s/he breathless while lying flat? Yes/No/don't know
9. Did s/he have wheezing? Yes/No/don't know

B. Questions pertaining to CARDIOVASCULAR system: (If response to Q1 is No/Don't know, skip to Q10)

1. Did s/he have chest pain? Yes/No/don't know (If yes for how long specify_____)
2. Did chest pain start suddenly or gradually? Yes/No/don't know
3. When s/he had severe chest pain, how long did it last? _____
4. Was the chest pain located below the sternum? Yes/No/don't know
5. Was the chest pain located over the heart and did it spread to the left arm or left jaw? Yes/No/don't know
6. Was the chest pain located over the ribs? Yes/No/don't know
7. Was the chest pain continuous or on and off? Continuous/On and off/don't know
8. Was the chest pain sudden in onset? Yes/No/don't know
9. Did chest pain get worse while coughing? Yes/No/don't know
10. Did s/he have palpitations? Yes/No/don't know

C. Questions pertaining to GASTROINTESTINAL system:

(If response to Q1 is No/Don't know, skip to Q5)

(If response to Q6 is No/Don't know, skip to Q9)

(If response to Q9 is No/Don't know, skip to Q13)

1. Did s/he have diarrhea? Yes/No/don't know (If yes for how long specify_____)
2. Was the diarrhea continuous or on and off? Continuous/On and off/don't know
3. When the diarrhea was most severe, how many times did s/he pass stools in a day? _____
4. Any associated symptoms with diarrhea _____
5. At any time during the final illness was their blood in stool? Yes/No/don't know
6. Did s/he have vomiting? Yes/No/don't know (If yes for how long specify_____)
7. When the vomiting was most severe, how many times did s/he vomit in a day? _____
8. What was the colour of the vomitus? Coffee colored/Bright red/Others/Don't know
9. Did s/he have abdominal pain? Yes/No/don't know (If yes for how long_____)

10. Where exactly was the site of abdominal pain? (Left/Right/Upper/Lower/All over/ don't know)
11. Did the abdominal pain radiate? Yes/No/don't know
12. If so, please specify where exactly did it radiate _____
13. Did s/he develop Jaundice? Yes/No/don't know
14. Did s/he develop black tarry stools? Yes/No/don't know
15. Did s/he have abdominal distension? Yes/No/don't know (If yes for how long specify_____
16. Did the distension develop rapidly within days or gradually over weeks or months? _____
17. Was there a period of a day or longer during which s/he did not pass stool? Yes/No/don't know
18. Did s/he have mass in the abdomen? Yes/No/don't know (If yes, for how long? Specify_____)
19. Where in the abdomen was the mass located? Encircle one or many as applicable (Right upper/Left upper/Right lower/Left lower/All over the abdomen/ Don't know)
20. Did s/he have difficulty or pain while swallowing solids? Yes/No/don't know (If yes, for how long? Specify_____)
21. Did s/he have difficulty or pain while swallowing liquids? Yes/No/don't know (If yes, for how long? Specify_____)

D. Questions pertaining to CENTRAL NERVOUS SYSTEM:

(If response to Q1 is No/Don't know, skip to Q7),

(If response to Q15 is No/Don't know, skip to Q22)

(If response to Q30 is No/Don't know, skip to Q34)

1. Did s/he have headache? Yes/No/don't know (If yes, for how long?_____)
2. Was the headache severe? Yes/No/don't know
3. Please describe the pattern, progression and distribution of headache_____
4. Did s/he have any accompanying symptoms with headache? Yes/No/don't know
5. If yes please specify the symptom _____
6. Did the headache affect his or her social activities? Yes/No/don't know
7. Did s/he have painful or stiff neck? Yes/No/don't know (If yes, for how long? Specify_____)
8. Did s/he have mental confusion? Yes/No/don't know (If yes, for how long? Specify_____)
9. Did the mental confusion start suddenly, quickly within a single day or slowly over many days? _____
10. Did s/he become unconscious? Yes/No/don't know (If yes, for how long? Specify_____)
11. Did the unconsciousness start suddenly, quickly within a single day or slowly over many days? _____
12. Did s/he have convulsions (mirgi/daura)? Yes/No/don't know (If yes, for how long?_____)
13. Was s/he unable to open the mouth? Yes/No/don't know (If yes, for how long? Specify_____)
14. Did s/he have stiffness of the whole body? Yes/No/don't know (If yes, for how long? Specify_____)
15. Did s/he have paralysis of one side of the body? Yes/No/don't know (If yes, specify which side: left/right and for how long _____)
16. Did the paralysis start suddenly, quickly within a single day or slowly over many days? _____
17. How did the weakness progress? Progressive/Intermittent/Step ladder/Others/Don't know

18. Did s/he have paralysis of lower limb(s)? Yes/No/don't know (If yes, for how long. Specify_____)
19. Did the paralysis involve one or both lower limbs? One limb/ both limbs (If one limb, which side limb specify: left / right / do not know)
20. Did the paralysis of lower limbs start suddenly, quickly within a single day or slowly over many days? _____
21. Did s/he have loss or disturbance in Gait/Balance? Yes/No/don't know
    If yes, please specify the pattern or type of gait _____
22. Did s/he have vertigo? Yes/No/don't know
23. Did s/he have diplopia? Yes/No/don't know
24. Did s/he have numbness over the face? Yes/No/don't know
25. Did s/he have slurring of speech? Yes/No/don't know
26. Was s/he suffering from diaphoresis (ghabrahat)? Yes/No/don't know
27. Was s/he suffering from bladder or bowel disturbances? Yes/No/don't know
28. Was s/he suffering from loss of sensation in any part of body? Yes/No/don't know (If yes, specify the location_____)
29. Was s/he suffering from abnormal sensations like paresthesia/tingling sensation etc.? Yes/No/don't know
30. If so, please describe the pattern of abnormal sensation as to how did it begin and progress and finally distribute itself? _____
31. Did the abnormal sensations start suddenly, quickly within a single day or slowly over many days? _____
32. Did s/he have preceding symptoms like headache/vomiting or fever? If yes specify _____
33. Was there any recorded fluctuation of pulse/blood pressure/dizziness/spells of syncope? If yes, specify. _____
34. Please give a timeline of the symptoms as to which came first to last and how did it progress? _____
    _____
    _____
    _____

E. Questions pertaining to GENITOURINARY system:

1. Did s/he have burning micturition? Yes/No/don't know
2. Was there any change in the colour of urine? Yes/No/don't know (If yes for how long_____)
3. Did s/he pass blood in urine? Yes/No/don't know (If yes for how long_____)
4. Was there any change in the amount of urine passed daily? Yes/No/don't know (If yes, for how long?) _____
5. Did s/he pass too much urine, too little urine or no urine at all or don't know? (encircle)
6. Did s/he wake up frequently at night to relieve urine? Yes/No/don't know
7. If yes how many times at night does s/he wake up to urinate? _____
8. Did s/he have flank pain with fever? Yes/No/don't know
9. Did s/he have suprapubic pain with fever? Yes/No/don't know

10. Did s/he have difficulty in initiating micturition? Yes/No/don't know
11. Did s/he have weak urine stream or hesitancy? Yes/No/don't know
12. Did s/he have urgency or inability to control urine or dribbling of urine? Yes/No/don't know
13. Please describe the timeline of symptoms from first to last and their pattern and progression

_____

_____

_____

_____

F. Questions pertaining to OTHER systems: (If response to Q1 is No/Don't know, skip to Q8)

1. Did s/he have skin rash? Yes/No/don't know (If yes, for how long _____)
2. Which sites were involved? Face/Trunk/Arms and legs/any other place_____
3. What did the rash look like? Measles rash/Rash with clear fluid/Rash with pus/Other/don't know
4. Where did the rash first appear? _____ _____
5. How did the rash progress, where did it start, progress and spread?

   _____
6. What was the type of lesion in the rash? Encircle below:
   Erythema/nodule/papule/macule/vesicle/pustule/petechiae/ecchymosis/abscess/ulcer/others_____
7. Was the rash associated with any symptom like fever or pruritus? Yes/No/don't know
8. Any history of other joint pain/myalgia? If so, specify the site and intensity _____
9. Did s/he have red eyes? Yes/No/don't know
10. Did s/he have bleeding from mouth/nose/anus? Yes/No/don't know
11. Did s/he ever have shingles or herpes zoster? Yes/No/don't know
12. Did s/he have weight loss? Yes/No/don't know (If yes for how long, specify _____)
13. Did s/he look thin and wasted? Yes/No/don't know
14. Did s/he have mouth sores or white patches in the mouth or tongue? Yes/No/don't know (If yes, for how long, specify _____)
15. Did s/he have any swelling? Yes/No/don't know (If yes for how long_____)
16. Where was the swelling present? Face/Joints/Ankles/Whole body/Any other please specify _____
17. Did s/he have any lumps? Yes/No/don't know (If yes for how long, specify_____
18. Where was the lump present? Neck/Arm pit/ Groin/Any other please specify _____
19. Did s/he have yellow discoloration of eyes? Yes/No/don't know. If yes for how long_____
20. Did s/he look pale (thinning or lack of blood) or have pale palms, eyes or nail beds? Yes/No/don't know
21. If yes for how long, specify _____
22. Did s/he have an ulcer, abscess or sore anywhere in the body? Yes/No/don't know. If yes for how long, specify _____
23. Where was the location of the ulcer? _____

Section 8: Treatment and health service use during the final illness:

1. Did s/he receive any treatment for the illness that led to death? Yes/No/don't know
2. Can you please list the drugs s/he was given for the illness that led to death (copy/provide the list from the hospital records)?_____ _____
3. What type of treatment did s/he receive? _____
4. Where did s/he receive the treatment? Home/ Traditional healer/ Govt clinic/ Govt hospital/ Private clinic/ Private hospital/ Pharmacy or drug seller store/Other _____
5. Did a doctor/health care worker tell you the cause of death? Yes/No/Don't know
6. What did the Doctor/ health care worker say:_____
7. Did s/he undergo any operation for the illness that led to death? Yes/No/don't know
8. On what part of the body was the operation? _____
9. How many days before death did s/he undergo the operation? _____

Section 9: Risk Factors:

(If response to Q1 is No/Don't know, skip to Q5)

(If response to Q5 is No/Don't know, skip to Q10)

1. Did s/he drink alcohol? Yes/No/don't know (If yes for how long_____)
2. How often did s/he drink alcohol? (Daily____/weekly_____/once a while/don't know)
3. Did s/he stop drinking alcohol? Yes/No/don't know
4. If yes, for how long before death did s/he stop drinking alcohol? _____
5. Did s/he smoke or chew tobacco? Yes/No/don't know (If yes for how long specify _____)
6. Mention the type of tobacco used: _____
7. How often did s/he smoke or chew tobacco? (Daily____/weekly_____/once a while/don't know)
8. How many cigarettes/beedi did s/he smoke or use chewing tobacco daily? _____
9. Did s/he stop smoking or chewing tobacco before death? Yes/No/don't know
10. Dis s/he use any other addiction (sniff/smoke/drugs/other) Yes/No/don't know
    If yes, for how long did s/he use addiction please specify_____
11. How often did s/he use any other addiction (sniff/smoke/drugs/other)? (Daily____/weekly_____/once a while/don't know)
12. Did s/he have any exposure to pesticides? Yes/No/don't know
13. Did s/he have exposure to indoor air pollution in terms of biomass fuel use? Yes/No/don't know

Section 10: Data abstracted from death certificate

1. Do you have the death certificate of the deceased? Yes/No/don't know
2. Can I see the death certificate (Copy the day, month and year of death from the death certificate) _____

3. Record the cause of death from the first (top) line of death certificate:

   _____

4. Record the cause of death from the second line of death certificate:

   _____

5. Record the cause of death from the third line of death certificate:

   _____

6. Record the cause of death from the fourth line of death certificate:

   _____

Section 11: Data abstracted from other health records

1. Are other health records available? Yes/No
2. Post mortem results (if any) _____
3. MCH/ANC card information _____
4. Hospital prescription information _____
5. Hospital discharge summary information _____
6. Laboratory results information _____
7. Other Hospital documents information if any _____
8. Cremation/burial information if any _____
9. Record the time at the end of the interview _____

Section 12: Miscellaneous

1. How do you think s/he had died? _____
2. What was the symptom s/he had before leading to death? _____
3. Do you know anyone who was with the deceased person just prior to death? _____
4. Was the autopsy done for the deceased person? (Yes /No) If Yes, date of autopsy_____

Facts and circumstances

5. Where was the body found?
6. What was the time the body was found?
7. What did you see around the body?
8. Did you see anything unusual around the body or on clothes?
9. What was the posture of the body when you saw it?
10. Was there any marks/bruises/injury/frothing/bleeding/fecal matter or any other substance on the body? (If yes please specify_____

Section 13. Bystander's/ person interested in sharing information

If any bystander/neighbour or any other person has information regarding the event or circumstances around the event, give details of the person and the information –

_____
_____
_____
_____
_____
_____
_____

Section 14: Interviewer's observations (To be filled at the end of the interview):

Any specific comments:

_____
_____
_____
_____
_____

Section 14: Final diagnosis:_____

Attach copies of all available documents (including case sheets, discharge summary, laboratory reports and postmortem reports)

Signature and Date	**Signature and Date**	**Signature and Date**
Name of interviewer:	**Name of interviewer:**	**Name of interviewer:**
Designation:	**Designation:**	**Designation:**
Contact no.:	**Contact no.:**	**Contact no.:**
Address:	**Address:**	**Address:**
Email Address:	**Email Address:**	**Email Address:**

Annexure 12: Conducting Autopsies in AEFI Deaths

Autopsy specimens in an AEFI case resulting in death

It is recommended that an autopsy in a death suspected to be due to an AEFI be performed as soon as possible (within 72 hours) to avoid tissue damage, development of post mortem artefacts and lysis of the adrenal glands, which can alter diagnosis.
The DIO should ensure that a detailed patient's history is included in the autopsy form that it is submitted to the team (autopsy surgeon/ pathologist/ forensic specialist) conducting the autopsy. The autopsy should be conducted as per the guidelines given to ensure that adequate effort is made to look for any underlying disease/pathologies in the deceased, which may be cause of death or contributed to the cause of death.

1. Background and Rationale:

The investigation of deaths due to AEFI would not be complete without an autopsy and related laboratory investigations. An autopsy must ideally be performed in every case of AEFI death. It may be considered as mandatory, especially in those instances when there has been previous reports of similar deaths that went uninvestigated, when public at large are worried about such deaths and are likely to lose or have lost faith in the vaccination programme, when there is a possibility of litigation and when such deaths have been attributed to vaccination anywhere else in the world.

2. Objectives of doing an autopsy in AEFI cases:

Autopsies done in program conditions are for forensic purposes. Hence the usual laid out procedures are followed without giving importance to specific needs of AEFI deaths. As indicated earlier it may not be possible to establish with certainty vaccination to be the primary or sole cause of death following immunization. The autopsy, on the other hand, may help to establish other causes of death and in a given circumstance may rule out vaccination to be the cause of death.
Thus, the role of autopsy would be:

- to establish whether death was due to a pre-existing natural disease including those that may be congenital or metabolic;
- to establish whether infection was a cause of death;
- to identify whether trauma, accident or otherwise could be a cause of death;
- to identify any other changes that may have contributed to death; and
- to identify anaphylaxis as a cause of death.

3. Process

Since by and large since most vaccinations are given during infancy, AEFI deaths would involve infants in most instances. The cause of immediate deaths attributed to the immunization procedure is most likely to be due to anaphylaxis. Since this causal relationship is invariably circumstantial and often arrived at when other causes are excluded, it is mandatory to investigate in a manner that ensures all possible causes for the death are systematically examined.

3.1 Timing of autopsy:

Since autolysis sets in early and the half-life of several cytokines related to anaphylaxis is

extremely short, all investigations of AEFI deaths must begin as soon as possible. The time frame for beginning an autopsy should be within two hours following death. Therefore the field worker or the Medical Officer in the field or at the hospital where the death may have occurred should seek the necessary permissions and arrange for the autopsy to be performed.

3.2 Location of where the autopsy should be performed:

Autopsy should be performed at a location where trained personnel are available and facilities to obtain and handle essential biological samples are available.

3.3 Consent for autopsy:

A proper consent should be taken for the autopsy. In those cases where the Government of India has made provisions for a mandatory autopsy, the family may be informed according to laid down procedures. The consent form should include consent for a complete autopsy, consent for examination of blood, body fluids, body tissues and organs.

3.4 Person who should be conducting the autopsy:

Ideally a trained pathologist or forensic medicine specialist should conduct such autopsies. However in usual program conditions, the medical personnel assigned this task should take up the procedure at the earliest possible.

3.5 Medical conditions to be considered during autopsy:

A large number of conditions may cause death during infancy and these need to be taken into account during investigation of an AEFI death. The investigation is always multidisciplinary.

3.5.1 Biological samples:

The team doing the autopsy must take following biological samples:

- Tissues/organs for histopathological examination
- Blood and body fluids for
  - » microbiological workup(bacterial/viral/others)
  - » Immunological and metabolic workup
  - » Haematological workup
  - » Toxicology workup
- Tissues for specialised investigations
  - » Genetic studies
  - » Electron microscopy
  - » Toxicology workup

3.5.2 Conditions:

The pathologist/ forensic specialist/other medical officer in-charge doing the autopsy should systematically look for conditions given in the following table:

List of conditions to be considered while doing autopsy of infants reported to have AEFI

General	Malnutrition Sepsis Disseminated Intravascular Coagulation Poisoning, drowning, scalding Hyperthermia (cystic fibrosis, congenital adrenal hyperplasia) Inborn errors of metabolism (Fatty acid oxidation defects)

Cardiovascular	Congenital Heart disease Myocarditis Trauma Coronary Arteritis (Kawasaki Disease) Anomalous arterial or venous drainage Cardiac tumours (Rhabdomyomas)
Respiratory	Epiglottitis Laryngotracheobronchitis Oedema of the larynx Bronchiolitis Pneumonia Pulmonary Hypertension Pulmonary Haemorrhage Atelectasis Bronchopulmonary dysplasia Impact of foreign body
Gastrointestinal tract	Enterocolitis Intestinal obstruction including volvulus, hernias etc Intestinal perforation and peritonitis Acute appendicitis Ruptured viscera with intraperitoneal haemorrhage
Liver	Hepatitis Fatty liver Cholestatic diorders Rupture
Pancreas	Acute pancreatitis
Kidney	Pyelonephritis Tubular necrosis Ischaemic injury
Brain	Cerebral trauma Intracranial haemorrhage Arteriovenous malformations Meningoencephalitis Evidence of hypoxia
Musculoskeletal	Skin, soft tissue, bone injury Soft tissue inflammation
Changes in certain specific conditions	*Sudden Infant Death Syndrome (SIDS)* • Tracheitis without isolation of pathogens • Infant found dead in the cot *Sudden Unexplained Death of Infancy (SUDI)* • Mild focal pulmonary haemorrhage • Older infant 2-5 month old found dead in the cot *Accidental or otherwise injury* • Fracture • Cranial injury *(Infant reported to have died. May have family history of abuse. May have died due to accidental injury from fall from the cot or by parents rolling over the baby)* • Anaphylaxis • Most often little or not findings(anaphylaxis kills by asphyxia or shock) • Laryngeal oedema • Pulmonary oedema • Myocardial infarction even in the absence of coronary artery disease • Congestion, widespread • Raised mast cell tryptase *(may be present for 3 days after death. Raised levels may be seen in other conditions including trauma)* • Raised total IgE or specific IgE

3.6 Requirements prior to autopsy:

The team doing the autopsy must be given a copy of all the records indicating clinical history, past medical history, congenital malformations, family history of similar events , drug history, immunization history, history of allergies and findings of medical records (including copy of CRF). Medical officer investigating the AEFI should also take history of the issues discussed in succeeding paras.

3.6.1 Documentation of sleeping environment (if found dead in the bed)

Asphyxia related

- Overlaying: Typically, when an infant shares the bed with adults, the adult may "roll-over" and choke the infant during sleep.
- Wedging: The infant may be choked when wedged between cushions or mismatched mattresses, etc.
- Choking: Any small object may result in choking.
- Obstruction to nose or mouth: Any object in the bed may accidentally obstruct breathing.
- Rebreathing: This happens in a closed environment created by a pocket of bedding or clothing.
- Neck Compression: Mechanical compression to the neck may occur by any object that is relatively heavy.
- Immersion in water: This may happen in unattended babies.

Sleep surface sharing

- Adults
- Children
- Pets

Recent sleep condition changes

- Change in position: Considered very important if within 24 hours of occurrence of the event
- Change in location
- Change in surface

Unsafe sleeping conditions potentially hazardous to cause asphyxia

- Soft, lumpy, concave sleeping surfaces
- Broken/mismatched beds, mattresses
- Worn/ torn/dirty/wet bedding

3.6.2 Documentation of possibility of hyperthermia / hypothermia

- Excessive or inadequate wrapping/ blanket/ clothing
- Excessive hot or cold environment

3.6.3 Documentation of environmental hazards

- Carbon monoxide
- Chemicals and sprays
- Electricity and devices
- Exposure to drugs, cigarette / beedi smoke, etc.
- Exposure to cords, strings, etc. that can entangle the baby

3.7 Facilities and equipment requirement for undertaking the autopsy

The following requirements are necessary in all cases:

- Proper autopsy room with adequate lighting and ventilation such that if required autopsies may be performed at night
- Availability of instruments for performing the autopsy and suturing the body after autopsy such that the body is returned to the nearest kin in a dignified and respectable manner for performance of final rites by the family
- Availability of sterile syringes and needles (10ml and 5ml with 21SWG and 22 SWG hypodermic needles)
- Availability of camera for photography and preferably videography of the autopsy itself for future review
- Plastic containers and buckets with lids for collection and storage of organs
- Adequate availability of 10% neutral buffered formalin
- Facilities for freezing tissues / samples on-site
- Facilities for separating plasma (at least a centrifuge must be available) as applicable

10% neutral buffered formalin	litre		5 litres		50 litre	
Formalin (Formaldehyde Solution 40% v/v or 37% w/v in water)	100	mL	500	mL	5	L
Tap water	900	mL	4.5	L	45	L
Sodium dihydrogen phosphate, monohydrate (NaH2PO4.H2O)	4.0	g	20.0	g	200	g
Disodium hydrogen phosphate, anhydrous (Na2HPO4)	6.5	g	32.5	g	325	g

- In case 10% neutral buffered formalin is not available at least 10% neutral formalin should be available:

10% neutral sodium acetate formalin	litre		5 litres		50 litre	
Formalin (Formaldehyde Solution 40% v/v or 37% w/v in water)	100	mL	500	mL	5	L
Tap water	900	mL	4.5	L	45	L
Sodium acetate (CH3COONa)	20.0	g	100.0	g	1000	g

- Availability of standard tubes for blood collection:
  - » yellow cap tubes for bacteriological culture
  - » red cap tubes for plain blood
  - » purple cap tubes for EDTA
  - » green cap tubes for Heparin
  - » grey cap tubes with Fluoride

3.8 Performing autopsy in AEFI deaths

The autopsy is generally performed by well-established and conventional techniques.

3.8.1 External Examination: Gross examination should include:

- Anthropometric measurements
- Recording any rigor mortis
- Examination for pallor, cyanosis, icterus
- Documentation of petechiae, bruises, injury
- Evaluation of site of vaccination
- Photograph of the infant in prone and supine position and of any findings especially injuries, in detail
- Radiograph of the infant wherever possible

3.8.2 Incision and evisceration

- Midline thoraco-abdominal incision
- Intermastoid incision for the skull
- Midline incision over the spine if the spinal cord is to be examined
- Evisceration of the organs is done by the Rokitansky technique after examination of the visceral contents and collection of blood, body fluids and samples for culture

3.8.3 Gross and microscopic examination especially for anaphylaxis

Histologically, the findings are essentially those that correspond to the gross findings: upper respiratory mucosal oedema and hyperinflation of lungs as well as congestion of various organs. In addition, eosinophil infiltration of the oedematous mucosa may be found.
Finding of numerous mast cells especially in the laryngeal mucosa is helpful. However the identification of mast cells require special stains such as toluidine blue or geimsa or immunohistochemistry. Special stains usually stain granules. Unfortunately, in most cases of anaphylaxis, the mast cells degranulate and hence the numbers may be grossly underestimated. Immunohistochemistry for CD117 and mast cell tryptase may be helpful in such circumstances.

No specific mast cell counts are available for normal. Numerous mast cells would definitely support the possibility of an allergic or anaphylactic reaction. However a recent study has shown that significant ($p < 0.05$) increase of both eosinophil granulocytes (mean 26.6 $\pm$ 17.8/SD/) and mast cells (3.2 $\pm$ 2.0/SD/) versus controls (eosinophils mean 7.0 $\pm$ 10.5 and mast cells mean 0.9 $\pm$ 1.1) were seen in splenic tissue in anaphylactic deaths. These figures need to be further evaluated in Indian subjects.

3.8.4 Laboratory Diagnosis

The following tests may be performed in case of suspected anaphylaxis.

1. Plasma IgE

- Usual method of detection: Quantitative immunofluorescent assay / radio allergo sorbent assay [RAST]
- Collection of specimen: blood in heparinised or EDTA vial
- Nature of specimen to be tested: plasma (separate plasma within 2 hours)
- Method of transportation: refrigerated
- Stability: ambient 48 hours, refrigerated 2 weeks, frozen 1 year
- Reference values vary depending on age (2-13 IU/mL at 0-5 months to 2-215 IU/mL for those above 18 years of age)

2. Plasma Tryptase [Total]

- Usual method of detection: Quantitative fluorescent enzyme assay
- Collection of specimen: blood in heparinised or EDTA vial
- Recommended site of collection: femoral vein
- Nature of specimen to be tested: Plasma (clotting may result in release from Basophils) Separate plasma immediately
- Method of transportation: frozen
- Stability: ambient 48 hours, refrigerated 72 hours, frozen 1 month
- Reference values 0.5-10.0µG/L
- Sample must be collected from 15mins -3 hours of the event

3. Whole Blood Histamine

- Usual method of detection: Quantitative enzyme-linked immunosorbent assay
- Collection of specimen: blood in heparinised vial.
- Nature of specimen to be tested: whole blood
- Method of transportation: frozen (critical)
- Stability: ambient 2 hours, refrigerated 6 hours, frozen 6 months
- Reference values: whole blood 180-1800 nmol/L

4. Plasma Histamine

- Usual method of detection: Quantitative enzyme-linked immunosorbent assay
- Collection of specimen: EDTA vial (plasma to be separated within 20 minutes: use upper two-thirds of plasma)
- Nature of specimen to be tested: plasma
- Method of transportation: frozen (critical)
- Stability: ambient 1 hour (Plasma), refrigerated 6 hours, frozen 6 months
- Reference values: whole blood 180-1800 nmol/L, plasma 0-8 nmol/L

5. Urine Histamine

- Usual method of detection: Quantitative enzyme assay
- Collection of specimen: ideal 24 hours (Not possible in Postmortem) freeze immediately
- Nature of specimen to be tested: urine
- Method of transportation: frozen
- Stability: ambient unacceptable, refrigerated 24 hours, frozen 6 months
- Reference values: urine: creatinine ratio 0-450 nmol/ G Creatinine
- 24 hours excretion: 0-60µG/day

3.8.5 Utility of tests:

- Plasma IgE: Useful in corroborating allergic reactions. Raised levels also seen in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), mastocytosis, hypereosinophilic syndrome.
- Plasma tryptase: Useful in anaphylaxis. ⍰ tryptase by radioimmunoassay may be a better option. Tryptase not reliable if collected after 3 hours of the event since the half-life is 2 hours.
- Whole blood / plasma histamine: Useful in anaphylaxis but sample must be drawn near the event (not practical in post mortem cases).
- Urine histamine: Better than whole blood / plasma histamine but a low level does not rule out anaphylaxis.

3.9 Post-mortem samples

Samples for microbiology, immunology, histopathology and virology, should be collected according to the instructions given by the relevant laboratories. All samples should be clearly labelled and dated. The request form should have the patient's information, a short history including clinical presentation, duration of illness and date of death. Indicate the necessary tests (if known) to be performed. In case special investigations are needed, contact the laboratory for instructions prior to sending samples. If possible mention the tentative / provisional diagnosis.

3.9.1 Histopathology

Samples for histopathology obtained from all major organs. Any macroscopically visible lesions should be described in detail and sampled extensively. Sample should be taken in 10% formal saline or in dry ice for frozen section. Specify the required special stains when necessary.

Central nervous system: Brain (If the brain is to be examined after fixation suspend in 20% formal saline for two weeks). Sections from middle frontal gyrus, hippocampus, basal ganglia (putamen+globus pallidus)+ insular cortex, mamillary bodies, thalamus, left cerebellum, dentate nucleus, mid brain, pons, and medulla should be obtained.
Cardio-vascular system: Myocardium (LV, RV, RA, LA, septum , other areas where relevant), cardiac valves, coronary arteries, conduction system and others
Respiratory system: epiglottis, tonsils, larynx, trachea, bronchi and lungs- (at least one sample from each lobe including hilum and periphery), hilar lymph nodes
Digestive system: liver, pancreas
Genitourinary system: kidneys including cortex and medulla
Mononuclear phagocyte system: spleen, thymus, bone marrow
Endocrine system: adrenal gland, pituitary, thyroid gland
Other: Injection sites including control, injuries and others

3.9.2 Microbiology

A: Bacteriological Investigation

Type of specimens and tests: blood for culture, CSF and body fluids for culture, pus for culture, tissues for culture and blood for serology

Collection and transport:

- Blood and body fluids for culture after death should be collected as early as possible and preferably before the body is sent to the morgue.
- If the body is already at post-mortem, following guidelines should be followed: blood, CSF and body fluids should be collected before the dissection is started. Follow standard precautions for collection of samples. Clean the overlying skin with 70% alcohol. Draw the sample using a sterile disposable needle and syringe. For blood culture, 3-5 ml blood (heart or venous) should be added into a blood culture bottle with 30-40 ml BHI and mixed carefully.
- CSF and other body fluids also should be sent in sterile screw-capped containers. These samples should be sent as soon as possible, at room temperature.
- Tissue samples should be sent in sterile normal saline in screw capped containers.
- Pus samples / swabs in sterile screw capped containers.
- Blood for serology and bacterial testing: plain blood in sterile containers.

B. Immunology

A post mortem sample for serum tryptase should be taken from femoral vessels, and not heart blood. Serum should be separated and stored at 40oC, or frozen if the assay is delayed. The circumstances regarding the death are important, as tryptase levels are also increased after myocardial infarction, trauma, amniotic fluid embolism and sudden infant death. Serum tryptase rises in anaphylaxis, if shock is present, or after insect stings, or in circumstances where the allergen enters the body parenterally. Anaphylaxis following ingestion of an allergenic food does not usually lead to an increase in tryptase levels.

Information on allergy to foods (particularly beef, pork, milk, gelatine, previous vaccination) should be obtained. A blood sample should be sent to the Medical Research Institute for testing for allergen specific IgE.

C. Mycological (fungal) investigations

- Blood: 5-10 ml of venous blood should be collected under strict aseptic precautions. The lid should be wiped with 70% alcohol before inserting the needle to inoculate the blood into a culture bottle containing Brain Heart Infusion (BHI) broth. Mix well and keep at room temperature till dispatched. Smaller volumes of blood from neonates should be collected into paediatric BHI bottles (1-5 ml). This should be sent as soon as possible to the laboratory.
- Bone marrow: 2-3 ml of bone marrow aspirate should be placed in a sterile screw capped container with 0.5 ml of 1:1000 heparin. Send within 24 hours to the laboratory.
- CSF: 3-5 ml of CSF should be collected into a sterile screw capped bottle.
- Body fluids: Chest, abdominal fluid and any drain fluid should be collected aseptically in a sterile screw capped bottle.
- Respiratory tract: Tissues should be collected into a sterile screw capped bottle containing normal saline. Another sample should be sent in formal saline for histology.
- Blood for serology: 1-2 ml of blood should be collected into a plain bottle.

D. Virology Investigation

General considerations: Most antigen / antibody detection assays in virology are compatible with serum / plasma. If the blood is haemolysed as it happens when blood is taken during the post mortem examination, these tests cannot be performed. Therefore it is recommended to the clinicians to take a blood sample just before or immediately after death if possible. Similarly other samples like CSF, lung tissue are recommended to be collected just before or after death. If the facilities are available, serum should be separated before transport.

It is recommended to take multiple specimens including blood, CSF, respiratory secretions, stool, lung tissue etc.

Pleural fluid, peritoneal fluid, pericardial fluid have limited value as antigen / antibody detection assays cannot be performed using these samples.

Tissue samples, swabs, respiratory secretions are collected into virus transport medium (VTM). VTM can be collected from the Department of Virology, MRI. It can be kept for few weeks at + 40o C (do not use if the colour has changed from yellowish orange to pink)

All samples, especially the samples intended for virus isolation / molecular assays should be collected with sterile precautions to prevent contamination (if tissue samples are taken, use separate sterile instrument set for each site).

E. Samples for electron microscopy

Mast cell degranulation is an important finding in allergy and anaphylaxis. Presence of this in myocardium especially around coronary arteries can be fatal and has to be differentiated from myocarditis. Therefore a section from the myocardium for this is essential and the sample should be 3mm thick tissue in glutaraldehyde.

Annexure 13: AEFI - Laboratory Request Form (LRF)

Annexure 13

AEFI – LABORATORY REQUEST FORM (LRF)
(To be completed by Drug Inspector/DIO. Vaccine/logistics sample should be sent with LRF)

AEFI category (Encircle): **Death / Hospitalized / Cluster / Disability/Others(specify)**_____

State		**Case ID** No.	**IND (AEFI) /** *State Code* / *District Code* / *Year* / *Serial*
District			
Block			

Name of Drug Inspector/DIO: Date of filling LRF :

Designation: Mobile No.:

Land Line (with STD Code) : Fax No.:

Case Name

Date of Birth | Age (in Months): (in days, if < 1 month) .....Days | ---- months | Sex (please tick) | ☐ Male | ☐ Female

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	*D D M M Y Y Y Y*	Date of Onset	*D D M M Y Y Y Y*
Date of collection of specimen	*D D M M Y Y Y Y*	Time of collection of specimen	*H H M M (AM PM)*

1. Precise description of samples:

a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

Mention vaccine/diluent	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufacturing Date	Expiry Date

b) For logistics specimens: (AD, Reconstitution, Disposable syringes)

Mention Logistics	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufacturing Date	Expiry Date

Name of AEFI Case:	**Case ID** **IND (AEFI)** / *State Code* / *District Code* / *Year* / *Serial No.*

c) For Biological sample/specimen: (CSF, Blood, Urine, tissue samples etc including post-mortem tissue samples if any)

S no.	Type of sample	Date	Laboratory name

2. Test requested:
3. Preliminary clinical diagnosis of District AEFI committee:

4. Name & complete address of officials to whom laboratory results should be sent:

Send to	Complete address	Phone/Fax	Mobile	Email-ID
State Drug Controller				
State EPI Officer				
State Cold Chain Officer				
District Immunization Officer (DIO)				
Immunization Division (MoHFW)				
Others (specify)				

Name of AEFI Case:	**Case ID** **IND (AEFI)** / *State Code* / *District Code* / *Year* / *Serial No.*

To be completed by lab officials after receiving the specimen								
Date of receipt of specimen at laboratory	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*
Name of person receiving specimen(s) at laboratory								
Condition of specimen upon receipt at lab (*encircle*)	Good*		Poor		Unknown			
Comments by pathologist, virologist or bacteriologist:								
Date specimen results sent from this lab	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*
Name of laboratory professional								
Signature								

Landline No. :	Fax No.:	Email Id:

**** Criteria for "good" condition: Samples sent as per AEFI guidelines.***

Annexure 14A: AEFI Causality Assessment Form (State)

STATE	DISTRICT	CASE ID	NAME OF PATIENT
AGE / SEX	**VACCINE (S) GIVEN**		**OUTCOME**

DATES & TIMES OF	IF DEATH CASE:
BIRTH: VACCINATION: FIRST SYMPTOM ONSET: HOSPITALISATION: DISCHARGE:	DATE & TIME OF DEATH: AEFI VERBAL AUTOPSY REPORT: YES/NO FIRST POST MORTEM REPORT: YES/NO FINAL POST MORTEM REPORT: YES/NO

AEFI FORMS RECEIVED	SUPPORTING DOCUMENTS RECEIVED	REMARKS
CRF: YES/NO CIF: YES/NO	HOSPITAL RECORDS: YES/NO DIAGNOSTIC REPORTS: YES/NO Others (name please):	

KEY FINDINGS AIDING ARRIVING AT VALID DIAGNOSIS:

Step 1 (Eligibility)

List all vaccines administered before this event	What is the valid diagnosis?	Diagnosis meets a case definition?
Level of certainty (if diagnosis included in Brighton's Collaboration):		

Create your question on causality here:

Has the_____vaccine / vaccination caused _____

(event for review in step 2-valid diagnosis)

Co-administered vaccines, if any:

Is this case eligible for causility assessment? Yes / No; If "Yes", proceed to step 2.

If "No", mention missing information required:

STATE	DISTRICT	CASE ID	NAME OF PATIENT

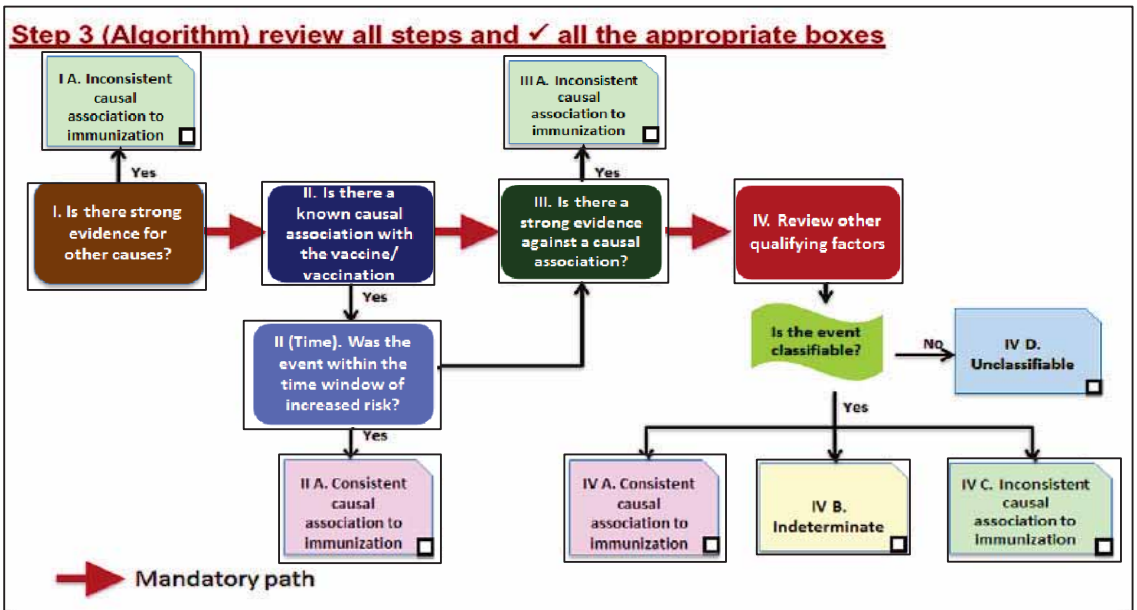
Step 2 (Event Checklist) √ (check) all boxes that apply

I . Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event even if administered correctly?	☐	☐	☐	☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐	☐	☐	☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐	☐	☐	☐	
Vaccine quality					
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐	☐	☐	☐	
Immunization Error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☐	☐	☐	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐	☐	☐	☐	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐	☐	☐	☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)	☐	☐	☐	☐	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☐	☐	☐	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☐	☐	☐	
Immunization anxiety (Immunization Triggered Stress Response - ITSR)					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction. hyperventilation or anxiety)?	☐	☐	☐	☐	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?					
12. In this patient, did the event occur within a plausible tme window after vaccine administration?	☐	☐	☐	☐	
III Is there strong evidence against a causal association?					
1. Is there a body of published evidence (systematic reviews. GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
1. In this patient. did such an event occur in the past after administration of a similar vaccine?	☐	☐	☐	☐	
2. In this patient did such an event occur in the past independent of vaccination?	☐	☐	☐	☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐	☐	☐	☐	
4 Did this patient have an illness, pre-existing condition or risk factor that could have contribute to the event ?	☐	☐	☐	☐	
5. Was this patient taking any medication prior to the vaccination?	☐	☐	☐	☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐	☐	☐	☐	

Y: Yes N: No UK: Unknown NA: Not applicable or Not available

STATE	DISTRICT	CASE ID	NAME OF PATIENT	OUTCOME

Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply

Adequate information available

A. Consistent with causal association to immunization

- ☐ A1. Vaccine product-related reaction (As per published literature)
- ☐ A2. Vaccine quality defect-related reaction
- ☐ A3. Immunization error-related reaction
- ☐ A4. Immunization anxiety-related reaction (ITSR**)

B. Indeterminate

- ☐ B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)
- ☐ B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent with causal association to immunization

C. Coincidental

- ☐ Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine

Adequate information not available

☐ **Unclassifiable**

Specify the additional information required for classification :

*B1: This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Summarize the classification logic in the order of priority:

With available evidence, we could conclude that the classification is _____because:

With available evidence, we could **NOT** classify the case because:_____

STATE	DISTRICT	CASE ID	NAME OF PATIENT	OUTCOME

Feedback on the case for district / others (specify):

S.N.	Name of experts	Designation	Signature	Date
1				
2				
3				
4				
5				
6				

Thank you

Notes: 1. All necessary documents should be available before the meeting.

2. Ensure that the Quorum is complete for state AEFI committee meeting.

3. All columns need to be filled.

4.Write N.A. if not applicable

Annexure 14B: AEFI Causality Assessment Form (National)

NATIONAL ID	STATE		DISTRICT
PATIENT'S NAME	**VACCINE (S) GIVEN**		**REASON FOR REPORTING**
VACCINATION BY (ROUTINE / CAMPAIGN)	**DATE OF BIRTH**	**AGE**	**DATE OF DEATH**
DATE OF VACCINATION	**DATE OF FIRST SYMPTOMS**	**DATE OF HOSPITALIZATION**	**OUTCOME**

Status of Case documents availability

(1) CRF (Yes / No) (2) CIF (Yes / No) (3) Hospital records (Yes / No/ NA) (4) Post Mortem (Yes / No /NA)

(5) Verbal Autopsy (Yes / No /NA) (6) State CA (Yes / No) (7) Other documents (Yes / No / NA).....

Documents availability checked & printed by - Name: ..... Date:..... Signature:.....

Case documents Screening status

Case screened by : Name: ..... Date: .....Signature: .....

Is this case a part of Cluster: Yes / No / NA, If Yes, Reported cluster / Indentified cluster No. of cases:

Final status of Case : F0 / F1 (If F0, mention reason) : .....

Case Summary:

Details of causality assessment by CA Sub & National committee (To be filled after CA Meeting)

	Valid Diagnosis	Classification
1. Valid Diagnosis & CA classification given by state AEFI committee		
2. Valid Diagnosis & CA Classification given by CA Sub committee experts		

3. Whether conclusion of CA Sub committee expert is consistent with conclusion of State AEFI Committee ? a) YES b) NO c) NA

If no, reason there of .....

4. Remarks (Quality review feedback by sub committee to State).....

Final Status of Causality Assessment

Details	Date		Status	Remarks (If F3 / F4)
Case discussed in CA Sub committee meeting			F2 / F3	
Case discussed in CA Sub committee meeting			F2	
Case discussed in NACM			F4 / F6	
Case discussed in NACM			F6	

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Step 1 (Eligibility)

Name Of the Patient	Name of one or more vaccines administered before this event	What is the valid Diagnosis?	Does the diagnosis meet a case definition?
«CHILD»			
Create your question on causality here **Has the_____vaccine/vaccination caused_____(the event for review in step 2-valid diagnosis)** **Co-administered vaccines, if any:**			

Is this case eligible for causility assessment? Yes / No; If, "Yes", proceed to step 2

Step 2 (Event Checklist) ✓ (check) all boxes that apply

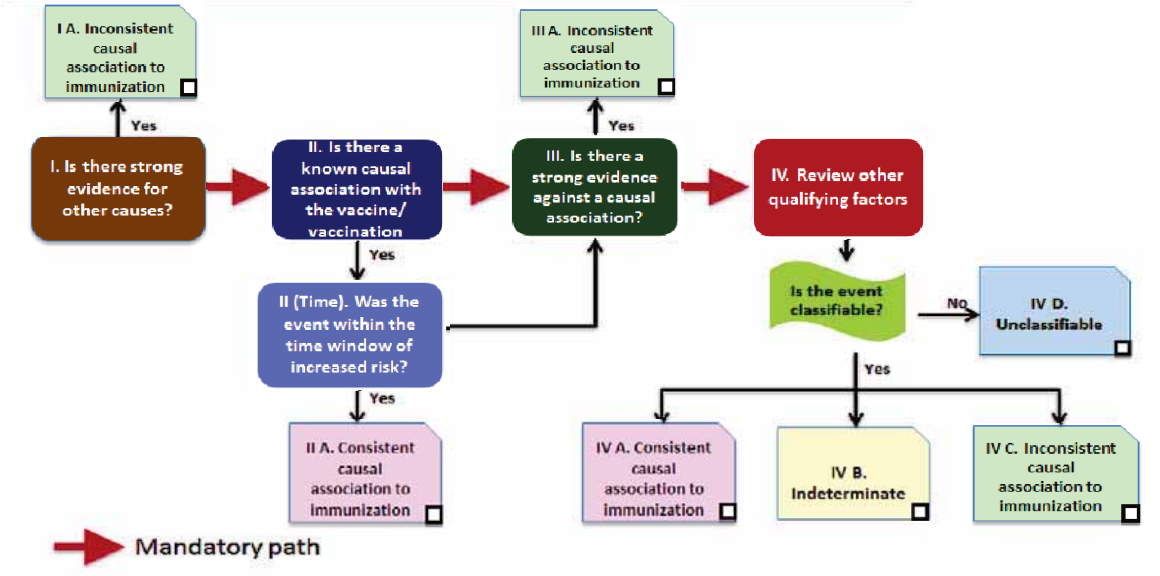
Step 2 (Event Checklist) √ (check) all boxes that apply					
I . Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
1. In this patient, does the medical history, clinical examination and/ or investigations, confirm another cause for the event?	☐ Y	☐ N	☐ UK	☐ NA	
II. Is there a known causal association with the vaccine or vaccination? (Vaccine product)					
Vaccine Product					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event even if administered correctly?	☐ Y	☐ N	☐ UK	☐ NA	
2. Is there a biological plausibility that this vaccine could cause such an event? https://bit.ly/3ecoAI0	☐ Y	☐ N	☐ UK	☐ NA	
3. In this patient, did a specific test demonstrate the causal	☐ Y	☐ N	☐ UK	☐ NA	
Vaccine Quality					
4. Could the vaccine given to this patient have a quality defect	☐ Y	☐ N	☐ UK	☐ NA	
Immunization Error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (eg.use beyond the expiry date,wrong recipient etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐ Y	☐ N	☐ UK	☐ NA	
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐ Y	☐ N	☐ UK	☐ NA	
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)	☐ Y	☐ N	☐ UK	☐ NA	
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐ Y	☐ N	☐ UK	☐ NA	
Imm. Anxiety- ITSR					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction. hyperventilation or anxiety)?	☐ Y	☐ N	☐ UK	☐ NA	

II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
12. In this patient, did the event occur within a plausible tme window after vaccine administration?	☐ Y ☐ N ☐ UK ☐ NA	
III. Is there strong evidence against a causal relationship ?		
1. Is there a body of published evidence (systematic reviews. GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event? https://bit.ly/3f8F1q6	☐ Y ☐ N ☐ UK ☐ NA	
IV. Other qualifying factors for classification		
1. In this patient. did such an event occur in the past after administration of a similar vaccine?	☐ Y ☐ N ☐ UK ☐ NA	
2. In this patient did such an event occur in the past independent of vaccination?	☐ Y ☐ N ☐ UK ☐ NA	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☐ Y ☐ N ☐ UK ☐ NA	
4 Did this patient have an illness, pre-existing condition or risk factor that could have contribute to the event ?	☐ Y ☐ N ☐ UK ☐ NA	
5. Was this patient taking any medication prior to the vaccination?	☐ Y ☐ N ☐ UK ☐ NA	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☐ Y ☐ N ☐ UK ☐ NA	

Y: Yes N: No UK: Unknown NA: Not applicable or Not available

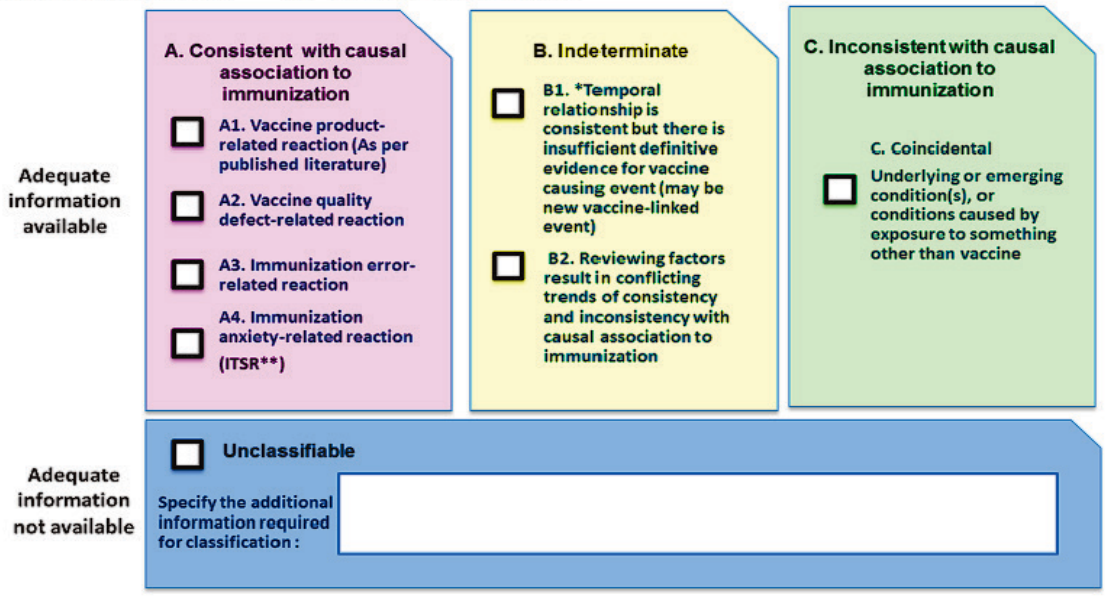
STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Step 3 (Algorithm) review all steps and ✓ all the appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply



Tick Reason for Unclassifiable:
1 Supporting documents (Hospital Records/ Post Mortem- Histopathology, Chemical analysis/ Verbal autopsy) not available
2. Documents are available but inadequate information in records.
3. Standard Reporting format (CRF/PCIF/FCIF) not available (incomplete documents)

*B1: This is a potential signal and maybe considered for investigation
** Immunization Triggered Stress Response

Summarize the classification logic in the order of priority:
With available evidence, we could conclude that the classification is _____because:

With available evidence, we could NOT classify the case because:_____

STATE	DISTRICT	NATIONAL ID
«STATE»	«DISTRICT»	«NATIONAL_ID»

Level of certainty as per Brighton's Classification (with reason for the same)

Feedback on the case for District / State / Others (specify):

S.N.	Name of Experts	Signature	Date
1			
2			
3			
4			

Annexure 15: ToR of District AEFI Committee

Every district must constitute and establish a functioning AEFI committee with District Immunization Officer as member secretary and a paediatrician/epidemiologist or public health specialist (govt./medical college) as the chairperson. The members in the committee should be locally available resource persons representing the above-mentioned fields wherever possible. The concerned block medical officers (in charge) where the AEFI has occurred and the MO who investigated/treated the case could be invited to the district AEFI committee on a case-to-case basis. The committee should meet at least once every quarter or earlier if needed. The membership of the committee may be reviewed once a year, so as to make sure that members are as per the recommended national AEFI guidelines. The quorum for each meeting is at a minimum of five members (two independent and three liaison members) including the chairperson, paediatrician and public health specialist.

The following are the terms of reference (TORs) of the District AEFI Committee:

1. Review AEFI Surveillance Status of the District

- Ensure reporting of at least ten serious and severe AEFIs per 100,000 live infants per annum in the district.
- Even if AEFI cases are not being reported from the district during the quarter, the district AEFI committee should meet to ascertain the reasons for the non-reporting and then take steps to address the issues.
- Inclusion of private and public tertiary and secondary care health facilities (medical colleges, district hospitals, nursing homes, clinics, dispensaries) in AEFI surveillance.
- Review the status of implementation of Quality Management System for AEFI surveillance in the district and follow up for achieving benchmarks eventually leading to state certification.
- Review status of AEFI trainings of health workers and medical officers in the district.
- Identification of silent blocks
- Review of availability and functionality of AEFI registers
- Assess the trends of minor, serious and severe AEFI reporting in AEFI registers and HMIS in the past one year

2. AEFI Case Investigation

- Support the DIO in conducting case investigation especially in case of deaths and cases reported in clusters
- Field visit and inspection of vaccination sites, cold chain stores, etc.
- Interviewing the AEFI case/relatives, treating doctors/staff and members of the block PHC/health facility, if required, to help in coming to an informed causality assessment
- Make suitable recommendations for prevention of recurrence of AEFIs based on results of investigations at the district level

3. Review of Document Completion Status for Causality Assessment of AEFI Cases

- Desk review of the completeness of CRF, CIF and supporting documents for causality assessment
- Analysis of similar cases or clustering of cases in the district
- Review the results of causality assessment conveyed from the state level and take necessary corrective actions at district level (especially for cases of immunization error)

4. Other Activities

- Support the spokesperson for media communication
- Ensure minutes of the meeting are shared with other members of the committee, the SEPIO and the sub-district levels within a fortnight of the meeting.

Annexure 16: ToR of State AEFI Committee

The State Immunization Officer (SEPIO) functions as the member secretary of the state AEFI committee and wherever feasible, a paediatrician/community medicine specialist/ medical epidemiologist (from the local government medical college or district hospital) should be made the chairperson. Specialists from medical colleges should to given preference to be inducted as members of the committee. During the meetings, while discussing cases for conducting causality assessments, the concerned district immunization officers and other members of the district AEFI committee where the AEFI has occurred could be special invitees when their cases are discussed for causality assessment. In case of any changes in the membership of the committee, a new notification should be issued by the state. These new members should undergo training in causality assessment and may be nominated by state EPI officer to attend the national causality assessment meeting for orientation on causality assessment processes. It is recommended that at least one third members of the committee should be rotated at least once in 3 years.

The committee should meet at least once every quarter or earlier as per need. The quorum for state AEFI committee meetings is at least 7 members (three independent and four liaison members) including the chairperson, paediatrician, public health specialist, forensic expert, microbiologist/pathologist.

The terms of reference of the State AEFI Committee are as follows:

1. Review AEFI Surveillance Status of State (and Districts)

- Ensure reporting of at least ten serious and severe AEFIs per 100,000 live infants per annum in the state.
- If no AEFI cases have been reported from the state during the quarter, the state AEFI committee should meet to ascertain the reasons for the non-reporting and then take steps to address the issues.
- Ensure district AEFI committees meet every quarter or more frequently as needed and that they fulfil their responsibilities
- Review districts for inclusion of private and public tertiary and secondary care health facilities (medical colleges, district hospitals, nursing homes, clinics, dispensaries) in AEFI surveillance.
- Review the status of implementation of Quality Management System for AEFI surveillance in the districts and state level and follow up for achieving benchmarks eventually leading to state certification.
- Review status of AEFI trainings of health workers and medical officers in the districts.
- Identification of silent districts.
- Review districts for availability and functionality of AEFI registers
- Assess the trends of minor, serious and severe AEFI reporting in AEFI registers and HMIS in the past one year
- Status of pending documents for reported AEFI cases

2. AEFI Case Investigation

- Supporting and guiding District AEFI Committees in conducting case investigation
- Field visit and inspection of vaccination sites, cold chain stores, etc.
- Interviewing the AEFI case/relatives, treating doctors/staff and members of the district AEFI committee, if required, to help in coming to an informed causality assessment

- Make suitable recommendations for prevention of recurrence of AEFIs based on results of investigations at the state level

3. Causality Assessment of AEFI Cases

- Desk review of the CRF, CIF and supporting documents for causality assessment
- Analysis of similar cases or clustering of cases in the state
- Causality assessment of cases and sharing the results at national level.

4. Other Activities

- Support the spokesperson for media communication
- Ensure minutes of the meeting are shared regularly with the AEFI Secretariat/ Immunization Division and AEFI Secretariat within a fortnight of the meeting. Minutes may also be shared with districts to convey the key actionable points for strengthening AEFI surveillance activities.

Annexure 17: Steps to Conduct Effective State AEFI Committee Meetings

A. Preparatory activities

- Seeking due approval for conducting the meeting and a draft agenda, at least two weeks prior to the proposed date of meeting.
- Circulating the meeting notice with draft agenda, to be shared with members of the State AEFI Committee members at least one week prior to the meeting.
- Preparing action taken report using the approved meeting minutes of last meeting
- Prepare a presentation on status of AEFI surveillance in the districts with updates on implementation of Quality Management System for AEFI surveillance and data on conduction of district AEFI committee meetings.
- Screening of cases for completion and preparation of case summaries supported by state AEFI technical collaborating centre.
- Checklist for meeting
    - (i) Agenda, approved minutes of last meeting, declaration and non-disclosure agreement formats, TA/DA claim forms – 15-20 copies
    - (ii) Attendance sheets
    - (iii) AEFI surveillance status report or presentation
    - (iv) Pending document status report
    - (v) Blank CA formats (depending on number of cases to be assessed)
    - (vi) One set of photocopies of cases for Causality Assessment
    - (vii) Causality Assessment tool kit (suitcase)
    - (viii) Stationary (as required – pens, notepads, etc.)
    - (ix) Audio-visual equipment (projector, screen, mikes, etc.),
    - (x) T equipment (computer and internet connection) for literature search

B. During the committee meeting

Update on AEFI surveillance status – The following are some of the key points related to surveillance that need to be reviewed:

- Action taken report of the SEPIO to discuss on actionable points of the last committee meeting.
- Status of silent districts (non-reporting/under reporting districts), AEFI related trainings
- Discussion on performance indicators related to AEFI surveillance and recommending actions to improve basic AEFI surveillance processes
- Update on progress of Quality Management System for AEFI surveillance activities in the state
- Operationalization of AEFI registers
- Discussion on frequency of District AEFI committees using district AEFI committee tracking tool to ensure these meetings are being held regularly
- Discussion on case completion status, mismatch in reporting of AEFI cases especially death cases in HMIS and state/national line list, involvement of ADR monitoring centre and private sector for reporting of cases.

C. During the Causality Assessment process

- Discussion on AEFI cases presented to the group of experts,
- Ascertaining the causality by consensus building,
- Filling up of causality assessment form
- Signature of experts (especially a paediatrician is mandatory) on the causality assessment form.

D. After the committee meeting

- Document all the programmatic discussion in form of minutes of meeting and circulate it to the members after due approval from the chairperson.
- Verify all the CA forms for completion, upload the scanned copies of the CA forms on SAFE-VAC to convey the results of the causality assessment to the national level.

Annexure 18: District Communication Plan for Immunization

District communication plan (DCP) for Routine Immunization												
Sr. No.	**Name of the state:**		**Name of District:**						**Name & Designation of Nodal Person for communication:**			
1	Advocacy	**DTFI meeting (One per Month)**	Numbers: person:			Responsible						
2		**Orientation/Sensitization of CSO partners**										
2.1		**Sensitization of Professional bodies such as IMA, IAP etc. (Twice per Year)**	Month…… Responsible person…….			Month…… Responsible person…….						
2.2		**Orientation of Religious leaders/Influencers (Twice per Year)**	Month…… Responsible person…….			Month…… Responsible person…….						
2.3		**Others**	Month…… Responsible person…….			Month…… Responsible person…….						
3		**District Media orientation workshops (Twice per Year)**	Month…… Responsible person…….			Month…… Responsible person…….						
4		**Any Other advocacy activity**	Month…… Responsible person…….						Specify:			
5	Capacity Building	**Training of block level health officers on communication Planning & Monitoring (Twice per Year)**	Month…… Responsible person…….			Month…… Responsible person…….						
6	Social Media	**Focal person for social media messaging**	Name & Designation of person:									
7		**Creatives for social media**	Yes/No, IF. If yes, Specify:									
8		**WhatsApp**	Number of groups formed…… Members…… Frequency……..									
9		**Any other**										
			District	Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7	Block 8	Total
10	Advocacy	**BTFI meeting for Immunization (One Per Quarter)**		Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	
11		**Meeting with key religious leaders/influencers at block level (Twice per Year)**		Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	

12	Capacity Building	**Orientation of ANMs /ASHAs/AWW on Communication planning (Twice per Year)**		Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	Month: Responsible Person:	
13		**Orientation of ANMs on IPC**										
14		**Orientation of ASHAs/AWWs on IPC**										
15	Social Mobilization	**Mother's meetings (One per Quarter per village)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
17		**Community meetings (VHSNC, SHGs, Mahila mandals for RI) (One per Quarter per village)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
18		**Rallies (One per Block per Quarter)**	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	Numbers: Responsible person:	
19		**Religious announcement including Mosque & Temple**		Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	Number of Religious institutions identified: Number of Religious institutions doing announcements:	
20		**Household visits for left out/ drop out families for IPC**		No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	No. of households identied and visited	
21	Mid media	**Posters (Five per village per Year)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
22		**Banner (One per session site per Year)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
23		**Hoardings (Three per Block per Year)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
24		**Leaflets (As required)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
25		**Wall paintings/ Slogan writing (One per village)**		Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	Numbers:	
26		**Miking/Local announcements (Twice a Year per Block)**		Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	Number: Responsible person:	
27		**Any other activity**										

Note I-This template will be completed by District MEIO/IEC officer/consultant. If there is no one dedicated for IEC activity, then District Immunization Officer will be responsible to compile with consultations of Block MOIC/BEE/IEC consultant and submit for the approval to the DTFI

Annexure 19: Media Rating Tool

- Has the source of the story (e.g. interview, conference, tip-off, document from some source, press release etc.) been stated?
- Has conflict of interest if any, been identified and declared?
- Does the story adequately describe the issue?
- Does the story report evidence to describe the issue?
- Does the story report on the economic aspects/ economic impact pertaining to the issue?
- Does the story explain/ describe benefits and harms pertaining to the issue?
- Does the story describe any alternative options available for the issue?
- Does the story go beyond the available media release?
- Are independent expert sources of information consulted and mentioned in the story?
- Is disease / scare-mongering avoided?
- Is the story presentable, readable, told in an understandable way and interesting enough to be read by a broad audience?
- Is it relevant to local settings?

Few examples of situation specific messages

- Benefits of immunization in preventing diseases are well proven.
- Un-immunised children are at greater risk of diseases and complications.
- Vaccine-preventable diseases cause millions of deaths and disability. Continued use of vaccines is the only solution to avert this situation.
- Vaccines do cause some reactions, but these are rarely serious and hardly ever cause long-term problems (have data ready and available to substantiate this fact).
- A surveillance system detects and is primed to investigate even the most minor suspected problems regarding immunization.
- The AEFI is being investigated, but the immunization programme must continue to keep the population safe from disease.

Some typical journalistic questions are given in Communication Guidelines for Building Vaccine Confidence around AEFI.
Please remember that no matter how provocative the tone of the question is, acknowledge the concern of the journalist and stick to your facts and respond in a cool manner.

Annexure 20: Sample District/State AEFI Response Template

..... DISTRICT/Place, ...STATE, DATE –

As a part of the Universal immunization program, the Government of .....(state) vaccinated _____(number of) children against vaccine preventable diseases including Polio, childhood TB, Diphtheria, Pertussis, Tetanus, Hepatitis B, Hib and Measles in the state between the months of _____-_____. The Government of ..... (state), through its ongoing efforts, has achieved an immunization coverage rate of _____% in _____ (year).

_____ (number of) doses of DPT/IPV/BCG/OPV (choose the vaccine/AEFI in question) have been administered to _____ number of children between (the dates) _____-_____.
As a part of the routine surveillance, _____ (number of) AEFIs have been reported on _____ (date) in district _____ (name of district), including _____ (details of case/s –e.g. 4 deaths, 3 hospitalizations) in _____ (month/s). The AEFI surveillance system records all minor adverse events (such as rashes, swelling at the injection site, fever etc) and investigates the serious cases (such as death and hospitalization) to strengthen the immunization program. The district AEFI committee is investigating the above cases with support from the state govt. All medical records are being reviewed/samples have been collected/post-mortems are being conducted/_____ (please add particulars of the relevant investigation/s).

AEFI surveillance is a reporting system to investigate the potential side effects after vaccination. Reporting an AEFI does not mean the vaccine has caused it. The cause can be determined only after proper investigation. There are wide ranging reasons for most side effects.

Vaccination has been recognized as the most effective public health intervention for child health, preventing disease mortality and morbidity. Every year, _____ (number of) infants/ under 5 years suffer from_____ (diseases/specific to antigen in question- depending the available data)) in the district. Manufacturing of vaccines is a tightly monitored process with multiple checks at different stages of production. Post production, each batch goes through tests to ensure quality and safety before they are released for use.

Annexure 21: Format for Key Messages and Supporting Messages

Key Message 1	Key Message 2	Key Message 3
Supporting message 1a	Supporting message 2a	Supporting message 3a
Supporting message 1b	Supporting message 2b	Supporting message 3b
Supporting message 1c	Supporting message 2c	Supporting message 3c

Annexure 22: Means of Media Communication

1. Press Statement

A press statement is used to convey a reaction to an event that has occurred. Assurances and the actions taken or intended to be taken is a part of it:

- A complete account of the event;
- An outline of actions taken to handle the event or planned to be taken (such as AEFI investigation);
- A description of the cause of the event;
- An assurance that corrective action has been taken or will be taken;
- Provide information on the 5Ws and 1H of media (when, where, who, what, why and how);
- Get more than one opinion on the issue at hand. Provide reference to any relevant publication, video material or website;
- Provide names and contact details of persons to be reached for additional information.

2. Press Release

The press release used when there is new information or an update. It must specifically answer the 5 Ws and 1 H for journalists:

- Who is affected/is responsible?
- What has happened? What is being done?
- When did it happen?
- Where has it happened?
- Why did it happen?
- How did it happen?

These may not necessarily be in the order given above. However, the contents should cover these questions. Mention names and contact details of district / state immunization officers, experts of the AEFI Committee members, IAP/IMA; name and contact details of the spokesperson for further details should journalists have more questions (at the end). Keep these ready. At the end of your communication with media, mention: "for more information, contact ..... (relevant person's name and designation), so that media can refer to the relevant person in case of any queries.

Steps for writing a press release is given in detail in Communication Guidelines for Building Vaccine Confidence around AEFI

3. Press Conference

Press conferences need to be used judiciously, as there is some risk, especially if there is lack of preparation and journalists are assertive. With different stakeholders being present, everything must be planned well in advance. Press conferences may need to be conducted if an AEFI is reported extensively and widely and there is a need to provide accurate facts and de-sensationalize the story. A press conference enables all journalists to have the same information, thus there is less likelihood of the event being 'sensationalized'.
For more details on Steps to be followed when preparing for a press conference, please refer to Communication Guidelines for Building Vaccine Confidence around AEFI

Prepare your speaker(s) to deliver your message

- Prefer to have one or two speakers during a press conference, to avoid overlaps with each other.
- Rehearse with the speaker(s) to make statements brief and clear and, usually no longer than 10 minutes.
- Speaker(s) should be experienced on the subject and able to respond to questions after the statement.
- Let the press know that the speaker is available after the press conference if anyone wants to interview
- Prepare your speaker(s) with 30-second answers for radio or TV, and quotable, simple messages for reporters.

4. Press Interview

Only a designated spokesperson should give the interview in routine as well as crisis situations. It is important that you find out who is conducting the interview and which organization he/she works for. The individual or their organization may have a particular point of view (for example, a bias in favour of or against vaccination), or they may have a reputation for fairness in news reporting.

Another consideration might be whether the interviewer has any prior medical or scientific training that may influence the kind of questions you could be asked. Most importantly, consider the emphasis you need to place on key messages you want to get across.

For more details refer to Communication Guidelines for Building Vaccine Confidence around AEFI (https://itsu.org.in/wp-content/uploads/2022/09/Communication_Guidelines_for_Building_Vaccine_Confidence_around_AEFI.pdf).

Annexure 23: Sample Press Release

Press Information Bureau

Government of India

Prime Minister's Office

03-July-2014 16:31 IST

THREE NEW VACCINES INCLUDING INDIGENOUSLY DEVELOPED ROTAVIRUS VACCINE TO BE PROVIDED TO ALL INDIAN CHILDREN

Fourth vaccine for adults to protect against Japanese Encephalitis to be introduced in high-priority districts

PM: Government will now ensure that the benefits of vaccination reach all sections of the society, regardless of social and economic status

The Prime Minister, Shri Narendra Modi, today announced the decision of the Government of India to introduce four new vaccines as part of India's Universal Immunization Programme (UIP). Vaccines against rotavirus, rubella and polio (injectable) will collectively expedite India's progress on meeting the Millennium Development Goal 4 targets to reduce child mortality by two-thirds by the year 2015 and meet global polio eradication targets. In addition, an adult vaccine against Japanese encephalitis will be introduced in districts with high levels of the disease.

Along with the recent introduction of the pentavalent vaccine, this decision represents one of the most significant policy leaps in 30 years in public health, preventing at least 1 lakh infant deaths, deaths of adults in working age group and up to 10 lakhs hospitalizations each year. With these new vaccines, India's UIP will now provide free vaccines against 13 life threatening diseases, to 27 million children annually, the largest birth cohort in the world.

The Prime Minister said "The introduction of four new lifesaving vaccines, will play a key role in reducing the childhood and infant mortality and morbidity in the country. Many of these vaccines are already available through private practitioners to those who can afford them. The government will now ensure that the benefits of vaccination reach all sections of the society, regardless of social and economic status."

Diarrhea caused by rotavirus kills nearly 80 thousand children each year, results in up to 10 lakh hospitalizations, pushing many Indian families below the poverty line. It also imposes an economic burden of over 300 crore rupees each year to the country. India has developed and licensed its first indigenous rotavirus vaccine, developed under a public-private partnership by the Ministry of Science and the Ministry of Health and Family Welfare. India will introduce this vaccine in a phased manner.

Tackling another major public health concern, the Government of India's Universal Immunization Programme is set to introduce a vaccine against rubella which causes severe congenital defects in newborns, like blindness, deafness and heart defects. It is estimated that nearly 2 lakh babies are born with congenital defects each year in the country.
The Universal Immunization Programme is also introducing an adult vaccine against Japanese Encephalitis (JE) in 179 endemic districts in 9 states. Reaffirming its commitment to the global goal of a polio free world, India is set to introduce Injectable Polio Vaccine (IPV), together with 125 countries in a globally synchronized manner. India has been certified polio free in March 2014, and the introduction of IPV in addition to the oral polio vaccine (OPV) will provide long lasting protection to the population against the virus.

Shri Narendra Modi, who has consistently placed an emphasis on health as part of the nation's development, said "India is committed to tackle child mortality and provide health for all through multiple initiatives taken up by the government. Strengthening routine immunization is an essential investment in India's children and will ensure a healthy future of the country."

The recommendations to introduce new vaccines have been made after numerous scientific studies and comprehensive deliberations by the National Technical Advisory Group of India (NTAGI), the country's apex scientific advisory body on immunization.

***

Backgrounder

India's Universal Immunization Programme is the world's largest immunization programme which aims to protect 27 million children born every year against 7 vaccine preventable diseases (tetanus, tuberculosis, diphtheria, pertussis, hepatitis B, measles and poliomyelitis) and Japanese encephalitis in certain districts where the disease is endemic and Haemophilus influenzae type b (or Hib which causes some severe forms of pneumonia and meningitis) in states where pentavalent vaccine has been introduced.

The Government of India provides free vaccines, syringes and needles to the states regularly. An entire cold chain system (with 27000 cold chain points) has been set up to ensure storage and transportation of vaccines in recommended temperatures. Vaccines are administered at government health facilities (hospitals, community health centres, primary health centres, dispensaries, sub centres) and outreach sessions in villages and urban areas on fixed days and fixed sites. Each year around 9 million sessions are held every year.

Note to The Editor

Vaccines against rotavirus and rubella and the injectable polio vaccine is being in the private sector for the past many years. The introduction of these vaccines in the Universal Immunization Programme makes it available to the poorer sections of society at no cost bringing in a level of equity. The introduction of the injectable polio vaccine is also a part of the end game strategy for global polio eradication. The vaccine against Japanese Encephalitis is already being given to children in districts from which Japanese Encephalitis disease has been reported. The same vaccine will now be offered to adults in districts reporting this disease among adults.

For more information, contact:
Ministry of Health & Family Welfare: Dr. - + 91-XXXXXXXXXX

Signal the end
##########

Annexure 24: National Immunization Schedule

NATIONAL IMMUNIZATION SCHEDULE (NIS)

for Infants, Children and Pregnant Women

as on 31 October 2023

Vaccine	When to give	Dose	Route	Site
FOR PREGNANT WOMEN				
Td-1	Early in pregnancy	0.5 ml	Intra-muscular	Upper Arm
Td-2	4 weeks after Td-1*	0.5 ml	Intra-muscular	Upper Arm
Td- Booster	If received 2 Td doses in a pregnancy within the last 3 yrs*	0.5 ml	Intra-muscular	Upper Arm
FOR INFANTS				
BCG	At birth or as early as possible till one yr of age	0.1ml (0.05ml until 1 month age)	Intra-dermal	Left Upper Arm
Hepatitis B - Birth dose	At birth or as early as possible within 24 hours	0.5 ml	Intra-muscular	Antero-lateral side of left mid-thigh
OPV-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1, 2 & 3	6 weeks, 10 weeks & 14 weeks (OPV can be given till 5 yrs of age)	2 drops	Oral	Oral
Pentavalent 1, 2 & 3	6 weeks, 10 weeks & 14 weeks (can be given till one yr of age)	0.5 ml	Intra-muscular	Antero-lateral side of left mid-thigh
IPV	Two fractional dose at 6 and 14 weeks of age	0.1 ml	Intra dermal two fractional dose	Right upper arm
Rotavirus	6 weeks, 10 weeks & 14 weeks (can be given till one yr of age)	5 drops	Oral	Oral
Pneumococcal Conjugate Vaccine (PCV)	6 weeks, 14 weeks & 9 completed months - booster	0.5 ml	Intra-muscular	Antero-lateral side of right mid-thigh In places where JE vaccine is administered, PCV Booster is to be given on Antero-lateral aspect of left mid-thigh

IPV-3	At 9 months	0.1 ml	Intra dermal	Left upper arm
Measles & Rubella (MR)	9 completed months-12 months. (can be given till 5 years of age)	0.5 ml	Sub-cutaneous	Right upper Arm
JE - 1**	9 completed months-12 months.	0.5 ml	Intra-muscular	Antero-lateral side of right mid-thigh
"Vitamin A (1st dose)"	At 9 completed months with measles- Rubella	1 ml (1 lakh IU)	Oral	Oral

FOR CHILDREN

DPT booster-1	16-24 months	0.5 ml	Intra-muscular	Antero-lateral side of left mid-thigh
Measles & Rubella (MR)	16-24 months	0.5 ml	Sub-cutaneous	Right upper Arm
OPV Booster	16-24 months	2 drops	Oral	Oral
JE-2	16-24 months	0.5 ml	Intra-muscular	Antero-lateral side of right mid-thigh
Vitamin A*** (2nd to 9th dose)	16-18 months. Then one dose every 6 months up to the age of 5 years.	2 ml (2 lakh IU)	Oral	Oral
DPT Booster-2	5-6 years	0.5 ml.	Intra-muscular	Left Upper Arm
Td	10 years & 16 years	0.5 ml	Intra-muscular	Upper Arm

*Give Td-2 or Booster doses before 36 weeks of pregnancy. However, give these even if more than 36 weeks have passed. Give Td to a woman in labour, if she has not previously received Td.

**JE Vaccine is introduced in select endemic districts after the campaign.

*** The 2nd to 9th doses of Vitamin A can be administered to children 1-5 years old during biannual rounds, in collaboration with ICDS.

Annexure 25: Indications for Adult Vaccinations

Vaccine*	Dose/Dosing	Indications	Precaution/Contraindication	Undesirable effects
Hepatitis A Vaccine (Hep A)[1,9] Inactivated vaccine	Two doses (first as primary and second booster); 1ml intramuscular The second (booster) should be given between 6 to 12 months after the primary dose	Recommended if the person is having HIV or Chronic Liver Disease	Persons with a known hypersensitivity to a component of the vaccine or to those who have shown signs of hypersensitivity during a previous administration of the same vaccine	Very common: pain and redness at injection site Common: swelling, malaise, fever (> 37.5°C)
Japanese Encephalitis (JE) [8,21] Inactivated JE virus protein	Two doses; 0.5 ml intramuscular Keeping a gap of at least one month between doses	Adults who are travelling to or living in regions where Japanese encephalitis is endemic or have a higher risk of exposure, such as travellers spending a month or longer in endemic areas or laboratory workers handling the virus	Severe allergic reaction (e.g. anaphylaxis) after a previous dose of the same vaccine	Fever, body ache, injection site pain, tenderness
Hepatitis B Vaccine (Hep B)[1,10] Subunit vaccine	Three or four doses depending on the condition Age 19 years or older – Three dose series (20mcg) at 0,1 and 6 months Four dose series (40 mcg) at 0, 1, 2 and 6 months for patients on haemodialysis	**Age 19 through 59 years**: Should complete a three-dose series if not vaccinated; **Age 60 years or older with** known risk factors for hepatitis B virus infection should complete a Hep B vaccine series; **Age 60 years or older without** known risk factors for hepatitis B virus infection may complete a Hep B vaccine series. **Risk factors for hepatitis B virus infection include:** • **Chronic liver disease** • **HIV infection** • **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen [HBsAg]-positive persons; men who have sex with men) • **Current or recent injection drug use**	Persons with a known hypersensitivity to a component of the vaccine or to those who have shown signs of hypersensitivity during a previous administration of the same vaccine	Pain and redness at injection site

Hepatitis B Vaccine (Hep B)[1,10] Subunit vaccine		• **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids; persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis; patients with diabetes, etc.) • **Incarceration** • **Travel in countries with high or intermediate endemic hepatitis B**		
Haemophilus Influenzae Type B Vaccine (Hib)[1,3] Protein Conjugate Subunit vaccine	One dose Three doses HSCT recipients only	Anatomical or functional asplenia (including sickle cell disease) Hematopoietic stem cell transplant (HSCT)	Persons with a known hypersensitivity to a component of the vaccine or to those who have shown signs of hypersensitivity during a previous administration of the same vaccine	Injection-site pain, redness, swelling, and fever
Human Papilloma Virus Vaccine (HPV)[1,11] **Protein subunit**	Three doses	Three doses within a span of six months (0, 2, 6) are recommended to all female adults upto 26 years of age Individuals aged 27 to 45 years, may take the vaccine upon shared clinical decision making	Hypersensitivity to the active substances or to any of the excipients of the vaccine. Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose	Injection site pain, and headache
Influenza Vaccine **Inactivated (Split Virion)[1,12]**	One dose annually (0.5ml intramuscular)	Any adult can take the vaccine	Contraindicated in person with history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine.	Injection site pain, headache, fever, cold, vertigo, nausea, body ache, myalgia, fatigue and vomiting

Vaccine	Dose/Dosing	Indications	Precaution/Contraindication	Undesirable effects
Rubella (R)[2] **Live attenuated**	One dose (0.5ml subcutaneous) A gap of at least one month should be given	Two doses of the vaccine are recommended for healthcare workers; in the setting of outbreaks; recent exposure to these infections; women who could become pregnant; and college students	Contraindicated in pregnancy and other immunocompromised conditions	Fever, lymphadenopathy, and arthralgia
Meningococcal[1] **(Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine**	One or more doses depending on indication1	Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, complement inhibitor (e.g., eculizumab, ravulizumab) use: may need a booster dose every 5 years if risk remains Travel in countries with hyperendemic or epidemic meningococcal disease, or microbiologists routinely exposed to Neisseria meningitidis	Severe allergic reaction (e. g, anaphylaxis) after a previous dose of a meningococcal capsular polysaccharide-, diphtheria toxoid- or CRM197-containing vaccine, or to any component of the vaccine. Persons previously diagnosed with Guillain-Barré Syndrome (GBS) may be at increased risk of GBS following receipt of the vaccine	Injection site pain, headache, and fatigue
Pneumococcal Conjugate Vaccine [1,3,13] **Pneumococcal Polysaccharide Conjugate Vaccine**	Single dose (0.5 ml intramuscular)	Age 65 years or more Age 19–64 years with certain underlying medical conditions or other risk factors which include alcoholism, chronic heart/liver/lung disease, chronic renal failure, cigarette smoking, cochlear implant, congenital or acquired asplenia, CSF leak, diabetes mellitus, generalized malignancy, HIV, Hodgkin disease, immunodeficiency, iatrogenic immunosuppression, leukaemia, lymphoma, multiple myeloma, nephrotic syndrome, solid organ transplants, or sickle cell disease or other hemoglobinopathies	Hypersensitivity to any component of the vaccine, including diphtheria toxoid.	Fever; injection-site erythema, induration/swelling or pain/tenderness; injection-site erythema or duration/swelling

Pneumococcal Polysaccharide Vaccine (PPSV23)[1,3,14]	One, two, or three doses depending on age and indication 0.5 ml intramuscular	Age 19 through 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease, diabetes), alcoholism, or cigarette smoking Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies): One dose PCV13 followed by one dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only one dose PPSV23 recommended at age 65 years or older)	Hypersensitivity to the active substances or to any of the excipients of the vaccine	Fever; injection-site erythema, induration/swelling or pain/tenderness; decreased limb mobility and peripheral oedema in the injected extremity
Poliovirus Vaccine (IPV) [1,15] **Inactivated**	Single dose	Travelers to countries where there is an increased risk of exposure to poliovirus may receive a one-time booster dose of IPV before traveling	Must not be administered to persons with a known hypersensitivity to one of the constituents of the vaccine nor to patients who had shown signs of hypersensitivity during a previous administration of inactivated polio vaccines	Pain, redness and swelling at the injection site, fever, loss of appetite, diarrhoea, vomiting
Tetanus and diphtheria toxoids and acellular pertussis Vaccine (Tdap/Td)[2,4,16]	Three primary doses (Tdap/Td) Two primary doses (Td) for pregnant woman	Td combination vaccine can be administered, two doses one-two months apart and a third dose after 6-12 months, with subsequent boosters at least once in every 10 years for long-term protection. Pertussis whole cell vaccine is not recommended for adolescents or adults. 1st dose: early in pregnancy 2nd dose: 4 weeks after first dose; if pregnancy occurs within 3 years of the last pregnancy, then only one dose is advised[4]	Hypersensitivity to the active substances or to any of the excipients of the vaccine	Fever, Malaise, Pain and tenderness at the injection site

Vaccine	Dose/Dosing	Indications	Precaution/Contraindication	Undesirable effects
Typhoid Vaccine (TCV)[5,17] **Typhoid (Vi Capsular Polysaccharide) conjugated on Tetanus Toxoid**	Single dose (0.5ml intramuscular)	Vaccination should be considered for professional food handlers in typhoid endemic areas, travellers from non-endemic going to endemic areas and clinical microbiology laboratory staff with a recognized risk of occupational exposure	Contraindicated in person having Hypersensitivity to any constituent of the vaccine, Pregnant and lactating women and in the event of fever or severe infection	Fever, pain at injection site and swelling
Varicella Vaccine (VAR)[2,18] **Live attenuated**	Two doses (0.5ml subcutaneous) The second dose should be given at least after 6 weeks but in no case less than 4 weeks	Varicella vaccine may be used either at an individual level to protect susceptible adolescents and adults. It may be offered to adolescents and adults without a history of varicella, in particular to those at increased risk of contracting or spreading the infection.	Contraindicated in subjects with primary or acquired immunodeficiency; who have a history of hypersensitivity to any of the constituents in the vaccine, or to neomycin In addition, pregnancy should be avoided in the month following vaccination	Redness, pain at the injection site swelling at the injection site, fever skin eruptions
Yellow Fever Vaccine[6] **Live attenuated**	1 dose (0.5 m subcutaneous)	Vaccination should be considered for travellers who are travelling to areas at risk for yellow fever virus[6]	Egg allergy; immune deficiency from medication or disease; symptomatic HIV infection; hypersensitivity to the previous dose; pregnancy	Rarely, encephalitis in the very young; hepatic failure. Rare reports of death from massive organ failure.

Zoster Vaccine Recombinant (RZV)[1,19]	Two doses (0.5 ml intramuscular) separated by two to six months	Age 50 years or older with or without risk factors Age > 19 years with some immunocompromised conditions (including HIV)	One should not get RZV if: • Has ever had a severe allergic reaction to any component of the vaccine or after a dose of Shingrix. • Currently has shingles. • Currently pregnant.	Mild or moderate pain, redness and swelling at the injection site Guillain-Barré syndrome (GBS), has been reported very rarely after RZV. A very small increased risk of GBS after having shingles exists.
Kyasanur Forest Disease Vaccine (KFD)[7]	Two doses at an interval of one month followed by periodic boosters after 6-9 months	Vaccination should be considered for persons living in at-risk areas or those travelling to such areas. Area to be considered for vaccination is 5-km radius of infected zone; aerial distance has to be considered not the road distance	Vaccine must not be administered to persons allergic to Gentamycin, Penicillin and Egg proteins. Vaccine should not be administered to those who are having fever, jaundice, and to pregnant women.	Slight burning sensation at the site of inoculation that lasts for one–two minutes. Do not rub the inoculation site. In some cases, mild giddiness may occur for two–three minutes post vaccination.

Vaccine	Dose/Dosing	Indications	Precaution/Contraindication	Undesirable effects
Rabies [20] **Cell Culture Vaccines** • Human Diploid Cell Vaccine (HDCV), Liquid (Adsorbed), 1ml • Purified Chick Embryo Cell Vaccine (PCECV), 1ml • Purified Vero Cell Rabies Vaccine (PVRV), 0.5ml and 1ml: • **Purified Duck Embryo Vaccine (PDEV), 1ml**	The course for Intramuscular **post-exposure prophylaxis** consists of intramuscular administration of five injections, one dose each given on days 0, 3, 7, 14 and 28. The course for intradermal route involves injection of 0.1ml of reconstituted vaccine per ID site and on two sites per visit (one on each deltoid area, an inch above the insertion of the deltoid muscle) on days 0, 3, 7 and 28. **Pre-exposure vaccination** is administered as one full dose of vaccine intramuscularly or 0.1 ml intra-dermally on days 0, 7 and either day 21 or 28	All animal bite victims of Category II and III exposures irrespective of age and body weight requires the same number of injections and dose per injection.	No absolute contraindication as the case fatality is 100%	Headache, malaise, nausea and fever. Minor and transient erythema, pain and/or swelling may occur at the site of injection, particularly following intradermal administration.

*This is only a collation of indications for adult vaccination from different sources. This is indicative and liable to change over time. Recommendations of treating doctor based on clinical judgement, availability of vaccines, and guidelines issued by the relevant authorities from time to time based on disease epidemiology and benefit-risk should to be considered for adult vaccinations.

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