Ministry of Health
& Family Welfare
Government of India

NATIONAL HEALTH MISSION
राष्ट्रीय स्वास्थ्य मिशन

AEFI

ADVERSE EVENT FOLLOWING IMMUNIZATION

Surveillance and Response

OPERATIONAL GUIDELINES

2015

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सत्यमेव जयते

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Government of India
Department of Health and Family Welfare
Ministry of Health and Family Welfare

Dated : 26th February, 2015

MESSAGE

India's Universal Immunization Program (UIP), targets almost 27 million newborns and 30 million pregnant women through 9 million sessions each year with the goal of protecting the individual and the public from vaccine preventable diseases. India is also the largest developing country manufacturer of vaccines in the world. It is the government's constant endeavor to not only to improve access, coverage and quality of immunization services but also target more diseases, causing infant and child morbidity and mortality by including newer vaccines that prevent them. Following the recommendation from the National Technical Advisory Group on Immunization (NTAGI) the pentavalent vaccine has been introduced in a phased manner while other vaccines such as inactivated Polio Vaccine (IPV), Rubella vaccine and Rotavirus vaccine are being considered for introduction.

Vaccines used in the country are safe and effective. However, like other pharmaceutical products, vaccines are not entirely risk-free and adverse events may occasionally follow vaccination. The Adverse Events Following Immunization (AEFI) Surveillance program indicates the government's intent to ensure the quality and safety of vaccines given in the country. Adverse events reported following immunization are not always related to the vaccine or the process of vaccination and are usually coincidental. However, to maintain public confidence, it is necessary to strengthen the surveillance of all adverse events following immunization (AEFI) by detecting, reporting and investigating such events to carry out further remedial actions.

I am thankful to all experts who contributed to the development of this guideline document. I hope this guideline will enable the health system to respond effectively to vaccine safety challenges by providing clear instructions regarding the roles and responsibilities of health staff in the field.

(B.P. Sharma)

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Dated: 26th February, 2015

FOREWORD

Intensive efforts are currently on-going in India to strengthen and intensify the routine immunization coverage and improve the quality of immunization services. Presently, approximately 27 million new born are targeted through nearly 9 million immunization sessions held annually. At the same time, new vaccines such as pentavalent vaccine have been added to the immunization program recently while some more, such as rotavirus vaccine, IPV and rubella vaccine, are going to be introduced soon. An increased use of vaccines (both in routine and mass immunization campaigns) has the potential of resulting in more adverse events following immunization.

Surveillance of AEFI involves a systematic collection of data on events following immunization and provides valuable information to help, plan and take necessary actions in order to sustain public confidence in vaccines and ensure smooth functioning of the programme. The Adverse Events Following Immunization (AEFI) Surveillance System in the country has come a long way since its inception in 1986. To strengthen the program, the National AEFI Secretariat has been established in 2012 with technical support and oversight from a National AEFI Technical Collaborating Centre in one of the leading medical institutions in the country. As Vaccine Preventable Diseases (VPDs) become less visible through effective immunization programmes, AEFIs become critical in building public trust in immunization.

I am happy that the Operational Guidelines for Surveillance and Response to AEFI have been revised to ensure use of standardised definitions and terminology in the country, in sync with Global AEFI Guidelines (2014). Past experience in the AEFI surveillance program has shown that lack of information regarding sequence of events in case of serious AEFIs can hamper decision making for vaccine safety. These guidelines introduce new verbal autopsy formats to ensure collection of valuable qualitative information about serious AEFIs in the field.

These Guidelines should help in further improving quality of investigations and causality assessment to allow for proper management and response to AEFIs leading to sustained vaccine confidence. I thank the National AEFI Committee and National AEFI Secretariat for their contributions in drafting the guidelines. The support of WHO India Country Office in development of these guidelines is highly appreciated.

(C. K. Mishra)

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PREFACE

Hundreds of millions of children have been immunized since the Universal Immunization Program was launched in 1985. These services are provided through network of fixed centres and outreach sessions covering rural and urban areas with reach to every village in the country. Although modern vaccines are safe, however, no vaccine is entirely without risk, and adverse events will occasionally occur following immunization. Increasing immunization coverage, mass campaigns and introduction of new vaccines and booster doses have increased vaccine use. Public alertness regarding vaccine safety has increased through awareness and increased access to information; it has led to more concerns about vaccine safety issues. Moreover, as Vaccine Preventable Diseases (VPDs) become less visible through effective immunization programmes, more attention will be given to Adverse Events Following Immunizations (AEFIs). Therefore, it is essential to report and investigate and assess each AEFI to determine whether a vaccine is causally linked to an AEFI or the reported AEFI is a mere coincidence or Immunization Error.

The first Operational Guidelines for AEFI Surveillance was published in 2005 followed by the second edition in 2010. Over the last couple of years, significant developments have been made in the field of immunization safety, both in knowledge and practices. This is the third revision of the AEFI Operational Guidelines and it uses globally standardized definitions and terminologies including new AEFI classification, revised formats for reporting, investigation, causality assessment and response and guidance for utilization of surveillance data and communication strategy on AEFI. The Guidelines are amply supplemented with concise tables and appendices that would support all tiers of medical and para-medical staff in AEFI Surveillance system. These guidelines should be used for reporting adverse events with any vaccines and not just those used in pediatric practice or in the Universal Immunization Program.

All health-care providers should be aware of different aspects of AEFIs and be prepared to respond to public concerns since timely response to public concerns about the safety of vaccines as well as prompt communication will preserve the trust of the community in the immunization programme. The objectives of these guidelines are to improve efficiency of surveillance activities of AEFIs, improve the quality of immunization services at the country and state levels, and, finally, to ensure immunization safety of all recipients of vaccines leading to achievement of goals and objectives of the immunization programme nationally and globally.

I am confident that this document would be helpful to use at national, state, district and sub district levels to improve the quality of immunization services. Further it will assure the government's commitment to provide quality health care services to each and every child of the nation.

(Dr Rakesh Kumar)

Contents

Abbreviations

AD	auto-disable
ADR	adverse drug reaction
AEFI	adverse event(s) following immunization
AFP	acute flaccid paralysis
ANM	auxiliary nurse midwife
aP	acellular pertussis
CBHI	Central Bureau of Health Intelligence
CDC	Centers for Disease Control and Prevention
CDL	Central Drugs Laboratory
CDSCO	Central Drugs Standard Control Organization
CGHS	Central Government Health Services
CHC	community health centre
CIF	case investigation form
CIOMS	Council for International Organizations of Medical Sciences
CRF	case reporting form
CRI	Central Research Institute
CSF	cerebrospinal fluid
DC	Deputy Commissioner
DCGI	Drug Controller General of India
DGHS	Directorate General of Health services
DIO	district immunization officer
EPI	expanded programme of immunization
EPID number	epidemiological number
FCIF	final case investigation form
GMP	good manufacturing practice(s)
GO	government order
GoI	Government of India
HHE	hypotonic-hyporesponsive episode
HMIS	Health Management Information System
IAP	Indian Academy of Paediatrics
ICD	International Classification of Disease

IDSP	Integrated Disease Surveillance Project
IgG	immunoglobulin G
IgM	immunoglobulin M
IMA	Indian Medical Association
IPC	Indian Pharmacopoeia Commission
IPHA	Indian Public Health Association
ITSU	Immunization Technical Support Unit
LAV	live attenuated vaccine
LRF	laboratory request form
MA	marketing authorization
MAH	marketing authorization holder
MCI	Medical Council of India
MO	medical officer
MoHFW	Ministry of Health and Family Welfare
NCC	National Coordination Centre
NCDC	National Centre for Disease Control
NPSP	National Polio Surveillance Project
NRA	National Regulatory Authority
NRHM	National Rural Health Mission
PATH	Prograanmme for Appropriate Technology in Health
PCIF	preliminary case investigation form
pH	acidity
PHC	primary health centre
PIP	project implementation plan
PMS	post marketing surveillance
PSUR	periodic safety update report
PvPI	Pharmacovigilance Programme of India
PVV	pentavalent vaccine
RI	routine immunization
RMP	rural medical practitioner
SEPIO	state expanded programme of immunization officer
SRA	state regulatory authority
SUAR	serious unexpected adverse reaction

SUIDI	sudden unexplained infant death investigation
TOR	term of reference
TSS	toxic shock syndrome
UIP	Universal Immunization Programme
VPD	vaccine preventable disease
VVM	vaccine vial monitor

1

Introduction

The goal of immunization is to protect the individual and the public from vaccine preventable diseases (VPDs). Although modern vaccines are safe, no vaccine is entirely without risk; and adverse reactions will occasionally occur following immunization. Adverse events following immunization (AEFI) are usually mild but may on rare occasions be life-threatening. The majority of serious events reported after immunization are coincidences and there is no causal relationship between the vaccine and the reported event. At times, however, these are caused by the vaccine or by an error in the administration or handling of the vaccine. Irrespective of the cause, when AEFI cause anxiety, people may refuse further immunization of their children, making the children susceptible to disabling and life-threatening VPDs.

Increased immunization coverage, mass campaigns and introduction of new vaccines and booster doses have increased vaccine use, leading to more vaccine reactions as well as more coincidental events. Immunization errors (previously known as “programme errors”) may also increase. Also, public alertness regarding vaccine safety has increased as a result of increased awareness and access to information through the electronic media. The vigilance of health-care providers on vaccine safety has increased due to strengthening of AEFI surveillance. As a result, more concerns on the quality and safety of vaccines are highlighted and/or expected by service providers and the public. Moreover, as VPDs become less visible through effective immunization programmes, more attention will be given to AEFI. Therefore, it is essential to report, investigate and assess each AEFI to determine whether a vaccine is causally linked to an AEFI or whether the reported AEFI is a mere coincidence.

Immunization safety covers the entire spectrum, ranging from vaccine manufacturing and regulation, vaccine safety and quality, safe injections and waste disposal and AEFI surveillance. AEFI surveillance refers to systematic collection of data on events following immunization. It provides valuable information to help plan and take necessary actions for AEFI in order to sustain public confidence in vaccine safety. Surveillance of AEFI is an effective means of monitoring immunization safety and can be used to identify and prevent immunization error-related reactions. It will also help distinguish a coincidental event from a true vaccine-related event. It guides the formulation of appropriate responses to reports of AEFI that can otherwise create a sense of crisis.

All health-care providers should be aware of the different aspects of AEFI and be prepared to respond to public concerns. Timely response to public concerns about the safety of vaccines, as well as prompt communication, will preserve the trust in the immunization programme.

These AEFI surveillance guidelines are a revised version of the AEFI Operational Guidelines, 2010 and are

in line with the revised WHO/Council for International Organizations of Medical Sciences (CIOMS) guidelines circulated in 2012–13. These guidelines will provide information to health-care providers and programme managers at national, state, district, block and primary health centre (PHC) levels for establishing a sensitive AEFI surveillance system. The key issues covered are:

- strategies and systems for ensuring quality and safety of vaccines in the country
- objectives of immunization safety and AEFI surveillance
- new classification of AEFI
- AEFI surveillance system—reporting, investigation, causality assessment and response processes
- optimum use of vaccine surveillance safety data
- communication strategy on immunization safety for public and media.

The objectives of these guidelines are to improve the efficiency of surveillance activities of AEFI, improve the quality of immunization services at the national and state levels and finally to ensure immunization safety of all recipients of vaccines leading to achievement of goals and objectives of the immunization programme in the country.

2

Principles of immunization and vaccines

2.1 Immunity

Immunity is the ability of the human body to tolerate the presence of material indigenous to the "body" (self) and to identify and eliminate "foreign" (non-self) material. This discriminatory ability provides protection from infectious diseases, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of an antibody to that organism. Immunity is generally very specific to a single organism or a group of closely-related organisms.

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

2.1.1 Active immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. It usually lasts for many years, often a lifetime. Active immunity is acquired if one survives infection from the disease-causing organism 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 they do not subject the recipient to the disease and its potential complications.

Many factors may influence the immune response of the body to vaccination. These include the presence of maternal antibody, 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.

2.1.2 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 unprotected individuals. The herd

immunity theory proposes that in the diseases which are circulated from one individual to another, the chain of infection breaks when large numbers of a population are immune. The higher the number of immune individuals, the lower is the likelihood that a susceptible person will come into contact with an infectious agent. From both theoretical and practical perspectives, disease usually disappears before immunization levels reach 100%, as has been seen with smallpox and poliomyelitis. The proportion of immune individuals in a population, above which a disease may no longer persist, is the herd immunity threshold. Its value varies with the virulence of the disease, the efficacy of the vaccine and the contact parameter for the population.

2.1.3 Passive immunity

Passive immunity is the transfer of antibody 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 up to a year.

2.1.4 How does immunization work?

There are many types of vaccines, but they all work in the same manner, i.e. 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-life memory lymphocytes that respond more quickly and in a more coordinated fashion to subsequent infections. As a result, the infectious microbe is destroyed more quickly. Protection is not always complete—an infection may not be always be prevented, but the severity of the illness is usually reduced.

The first exposure to a vaccine stimulates the immune response of body (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.

Subsequent administration of the same vaccine stimulates the secondary response. The secondary response is much faster than the primary response and predominantly produces IgG 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.

Primary and secondary responses to an antigen are given in Figure 2.1.

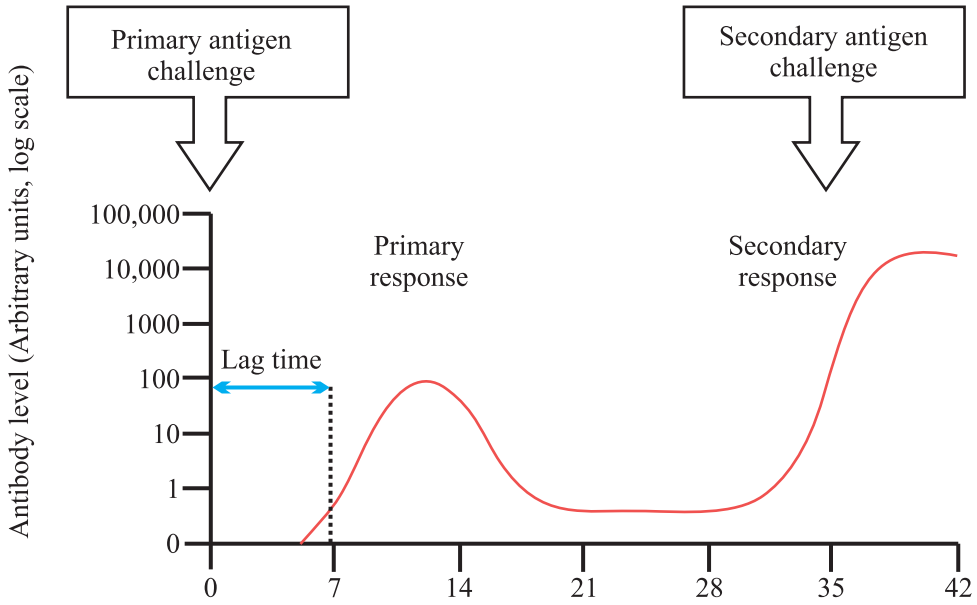

Fig. 2.1 Primary and secondary response to an antigen

Secondary response may be more effective, eliminating pathogens before any damage occurs

2.2 Vaccine

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

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 polio vaccine.

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, reducing cold chain storage space, improving compliance (by reducing the number of pricks involved in administering separate vaccines), reducing the cost of extra health-care visits and improving timeliness of vaccination, thereby facilitating the addition of new vaccines in immunization programmes.

No evidence exists 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 types of vaccines: 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.

Live attenuated vaccines

Live attenuated vaccines (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. The resulting vaccine organism retains the ability to replicate in the vaccinated person and produce immunity, but usually does not cause illness. The immune response to a LAV is virtually identical to that produced by a natural infection.

When using 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 ensure that nearly 100% of recipients are immune (i.e. the second dose is "insurance"). Immunity following live vaccines is long-lasting and booster doses are not necessary, with the exception of oral polio vaccine, which requires multiple doses. LAVs are labile and can be damaged or destroyed by heat and light. They must be handled and stored carefully. Currently available LAVs include measles, mumps, rubella, varicella, yellow fever, oral polio and influenza (intranasal). Live-attenuated bacterial vaccines include BCG and oral typhoid vaccine.

Inactivated whole-cell vaccines

Inactivated 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 live, they cannot grow in a vaccinated individual and, therefore, cannot cause the disease, even in an immunodeficient person. Inactivated vaccines are thus generally safer than LAVs. Unlike live antigens, inactivated antigens are usually not affected by circulating antibodies. They are often more stable than LAVs.

Growing whole bacteria such as whole-cell pertussis vaccine or viruses such as inactivated poliomyelitis vaccine in culture media, then treating them with heat and/or chemicals, produces an inactivated, non-viable vaccine.

Inactivated vaccines always require to be administered in 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 live vaccines, 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 titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase or "boost" antibody titers.

Subunit vaccines

Instead of the whole microbe, subunit vaccines include only those antigens that best stimulate the immune response. Because subunit vaccines contain only the essential antigens and not all the other components of the microbes, chances of adverse reactions are lower. Subunit vaccines can be produced in two ways:

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

Depending upon the type of antigens, subunit vaccines can be of three types.

Protein-based vaccines

Subunit vaccines can be protein-based. For example, 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 and used 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).

Polysaccharide vaccines

Meningococcal and pneumococcal polysaccharide vaccines contain the polysaccharide coats, or capsules, of encapsulated bacteria which are purified and made non-infectious.

Conjugate vaccines

Many bacteria have a polysaccharide outer wall. The immature immune system of children under 2 years of age does not respond well to 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 T-cells recognize, then these conjugate vaccines can elicit strong immune responses and immune memory in young children.

Toxoid vaccines

In some bacterial infections such as diphtheria or 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 are given in Figure 2.2.

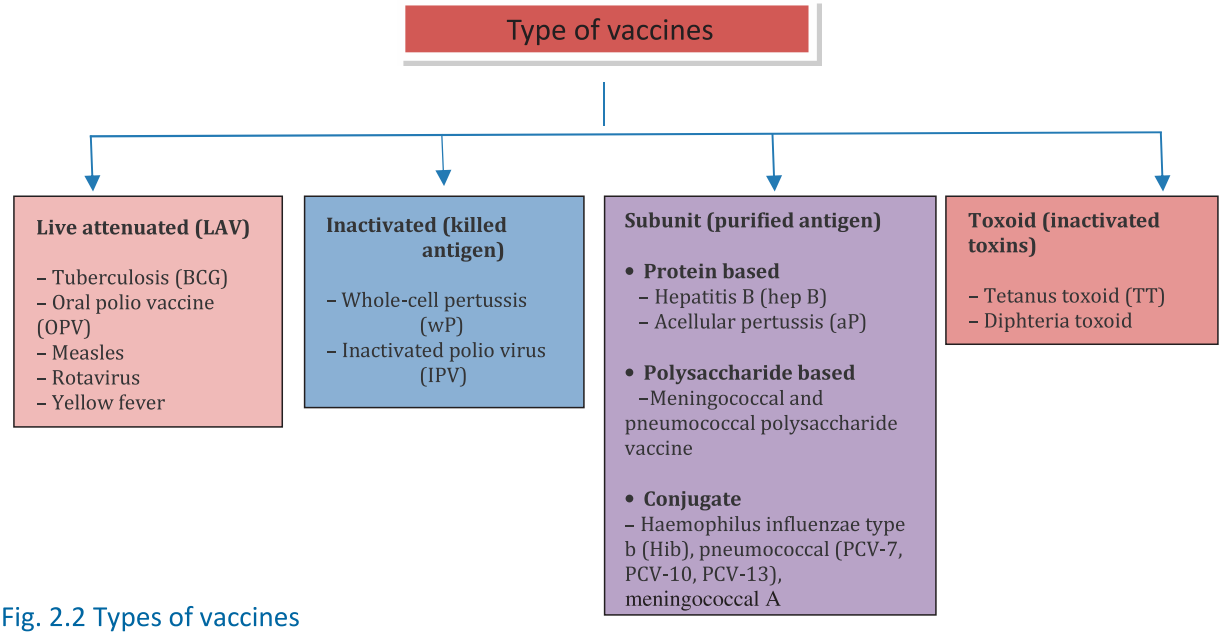

Fig. 2.2 Types of vaccines

2.2.2 Other components in vaccines (excipients)

Adjuvant

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 sulfate) which primarily enhance the immune response to proteins. They have been shown to be safe over several decades of use. In rare cases, 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 contain less than 25 μg of neomycin per dose (less than 0.000025 g). 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 or 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 confirm product quality or stability, compounds may be added to vaccines for a variety of manufacture-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.

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 amounts present are 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 wherein the risk ofoccurrence of a serious adverse reaction increases. Ignoring contraindications can lead to avoidable vaccine reactions. One of the worst and most serious vaccine reactions is anaphylaxis. Most contraindications are temporary and the vaccine can be administered at a later time. The only contraindication applicable to all vaccines is a history of a severe allergic reaction to a prior dose of vaccine or to a vaccine constituent.

Precautions are not contraindications but are events or conditions to be considered in determining if the benefits of the vaccine outweigh the risks (especially if the would-be recipient is an immunocompromised or pregnant person). Precautions stated in the product labelling can sometimes be inappropriately interpreted as absolute contraindications, resulting in a missed opportunity to vaccinate.

Summary

- Immunity is described as the body's protective ability against disease. There are two basic mechanisms for acquiring immunity: active and passive.
- Active immunity can be either natural, following an infection, and can last a lifetime, or through vaccination, which also lasts for a long period.
- Passive immunity also can be either natural or artificial; both last for a relatively shorter period.
- Vaccine is a biological product that improves immunity to a given disease and is divided into four types: live-attenuated, inactivated whole cell (killed), subunit and toxoid.
- Excipients (adjuvant, preservatives and other additives) contained in vaccines can cause occasional reactions. Their knowledge is important in immunization safety surveillance.

3

AEFI basics

Vaccines used in national immunization programmes are extremely safe and effective. Nevertheless, no vaccine is perfectly safe, and adverse reactions can occur. In addition to the vaccines themselves, the process of immunization is a potential source of an adverse reaction.

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

Reported adverse events can either be true adverse events, i.e. actually 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.

In 2012, the CIOMS and WHO revised the existing classification to make it relevant to cause-specific categorization of AEFI (Table 3.1).

Table 3.1. Cause-specific categorization of AEFI (CIOMS/WHO 2012)

Cause-specific type of AEFI	Definition
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine 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 AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

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.

3.1 Vaccine reactions

Based specifically on the cause, severity and frequency, vaccine reactions may be grouped into two broad categories:

(i) **Cause-specific vaccine reactions**

(a) Vaccine product-related reaction

(b) Vaccine quality defect-related reaction.

(ii) **Vaccine reactions by severity and frequency**

(a) Common minor reactions

(b) Serious and severe vaccine reactions.

3.1.1 Cause-specific vaccine reactions

The new cause-specific categorization is important for decision-making on a vaccine product, since it clearly differentiates between the two types of possible vaccine reactions.

A *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 an immune-mediated reaction of the individual or replication of a vaccine-associated microbial agent, e.g. attenuated live virus. Immune-mediated reactions are generally mild. However, it is important to note that among certain high-risk individuals, there is a tendency of an immune-mediated reaction triggering adverse reactions which do not occur in the majority of vaccinees. For example, fever is a common minor reaction following vaccination, but the same can trigger seizures among children with an underlying seizure disorder.

A *vaccine quality defect-related reaction* is the defect in a vaccine that has 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 a wild type vaccine agent, e.g. wild polio virus during the manufacturing process or a contaminant introduced during the manufacturing process could cause a vaccine quality defect-related reaction. In the early years of immunization

Case Study	In 1955, after administration of the inactivated 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. ***Cause:*** Vaccine quality defect-related reaction http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/

programmes, a few major incidences of vaccine quality defect-related reactions were reported. However, with the introduction of good manufacturing practices (GMPs) and strengthening of the national regulatory authorities, the potential risks of such quality defects are now very low and such occurences are extremely rare.

3.1.2 Vaccine reactions by severity and frequency

Most vaccine reactions are minor and self-limiting. More serious reactions are very rare and in general do not result in long-term problems. Categorization by frequency of occurrence is given in Table 3.2.

Table 3.2. Categorization of reported adverse reactions by frequency of occurrence

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

Common minor vaccine reactions

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 part of the immune response. In addition, some of the vaccine's components such as adjuvants, stabilizers or preservatives can lead to a reaction. An effective and safe vaccine produces the best possible immunity and reduces these reactions to a minimum. The proportion of frequency of reactions likely to be observed with the most commonly used vaccines are listed in Table 3.3.

Table 3.3 Frequency and nature of minor vaccine reactions

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)	up to 50%	Up to 50%	Up to 55%
Pnemucoccal	~ 20%	~ 20%	~ 20%
Tetanus/DT/aTd	~ 10%	~ 10%	~ 25

The occurrence of local reactions such as pain, swelling and/or redness at the injection site varies for the type of antigen. For example, whole cell DTP has reported these local reactions as very common (>10%), whereas for acellular DTP it is only a common reaction with a frequency of 1%–10%. 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 for the type of antigen. Fever is a very common systemic reaction (>10%) reported for most antigens. Other common systemic reactions (irritability, malaise, loss of appetite) can also occur after many antigens. DTwP has more reports of these systemic reactions than DTaP. For LAVs 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. However, in case of any significant increase of these observed rates over that expected for any vaccine, an investigation is needed to exclude a possible adverse reaction to the given vaccine. Further, these reports may also differ from those outlined in the manufacturer's package information and therefore these rates need to be cautiously interpreted.

SEVERE AEFI

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

Serious and severe vaccine reactions

"Serious" and "severe" are often used as interchangeable terms, but they are not. An AEFI will be considered "serious" if it meets any of the following criteria: results in death, is life-threatening, requires inpatient hospitalization or if prolongation of existing hospitalization results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage. "Severe" is used to describe the intensity of a specific event (as in mild, moderate or severe). The event itself, however, may be of relatively minor medical significance. For example, fever is a common relatively minor medical event, but according to its severity it can be graded as mild fever or moderate fever. Anaphylaxis

is always a serious event and life-threatening. Most of the rare and more serious vaccine reactions (e.g. seizures, thrombocytopenia, hypotonic-hyporesponsive episodes (HHEs), persistent inconsolable screaming) do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects.

Vaccine	Reaction	Onset interval	Frequency per doses given
BCG	Fatal dissemination of BCG infection	1–12 months	0.19–1.56/1.000.000
OPV	Vaccine associated paralytic poliomyelitis (VAPP)**	4–30 days	2–4/1.000.000
DTwP	Prolonged crying and seizure	0–24 hours	< 1/100
	HHE	0–24 hours	< 1/1.000–2/1.000
Measles	Febrile seizures	6–12 days	1/3.000
	Thrombocytopenia	15–35 days	1/30.000
	Anaphylaxis	1 hour	1/100.000
Rotavirus	Intussusception	3–14 days	1–2/100 000

Table 3.4. Frequency and nature of severe/serious vaccine reactions

3.1.3 Prevention and treatment of vaccine reactions

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, vaccines are contraindicated if there is a possibility of serious allergy to a vaccine or its components.

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 actions will help to reassure parents about immunization and prepare them for common reactions. Antipyretic drugs can be given in a dosage and schedule as recommended by the prescriber (or manufacturer). For example, paracetamol in a dose of up to 15mg/kg every 8 hours with a maximum of four doses in 24 hours is useful for the common minor reactions to DTP vaccine; it eases pain and reduces fever. However, it is important not to overuse paracetamol or any other antipyretic drug as overdosing may harm the vaccinee. A febrile child can be cooled with a tepid sponging or a bath, and by wearing light, cool clothing. Extra fluids need to be given to children with fever. For local reactions, a cold cloth applied to the site may ease the pain.

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

It is recommended that facilities be available at all clinical settings to provide initial emergency care in case of an adverse event. Following vaccination, parents should be advised to wait for at least 30 minutes at the site. All immunization providers need to be trained and develop competence in managing

anaphylaxis. Availability of adrenalin and other basic items for resuscitation is vital. It is also important to ensure a continuous supply of adrenaline and its timely replacement on expiry (refer Annexure 11).

3.2 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—handling, prescribing and administration of the vaccine.

Note: This AEFI type was earlier categorized as "programme error".

Immunization error-related reactions are preventable, and they derail the benefit of the immunization programme (Table 3.5). The identification and correction of these errors in a timely manner is therefore of great importance.

Table 3.5 Types of Immunization error-related reactions

Immunization error		Related reaction
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)	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	Failure to protect as a result of loss of potency or non-viability of an attenuated product
Error in vaccine prescribing or non-adherence to recommendations for use	Failure to adhere to a contraindication	Anaphylaxis, disseminated infection with an attenuated live vaccine, VAPP
	Failure to adhere to vaccine indications or prescription (dose or schedule)	Systemic and/or local reactions, neurologic, muscular, vascular or bony injury due to incorrect injection site, equipment or technique
Error in administration	Use of an incorrect diluent or injection of a product other than the intended vaccine	Failure to immunize due to incorrect diluent, reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent
	Incorrect sterile technique or inappropriate procedure with a multi-dose vial	Infection at the site of injection/beyond the site of injection

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

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

The symptoms arising from an immunization error may help to identify the likely cause. For example, children immunized with contaminated vaccine (usually the 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, can confirm the source of the infection.

Sterile abscesses are rare local reactions (~1 per 100 000 doses) from aluminium containing vaccines, especially DTP. Inadequate shaking of the vaccine before use, superficial injection and use of frozen vaccine, all increase the risk of sterile abscess and of local reactions. Contamination of vaccine or injection equipment can also lead to a bacterial abscess. For BCG vaccine, injection abscess can arise from an improper technique of injection (subcutaneous rather than intradermal injection).

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

Healthcare workers also need to have a clear understanding of the 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 a case-based assessment.

Open vial policy

Follow the open vial policy which is applicable to DPT, hepatitis B, tetanus toxoid, oral polio and liquid pentavalent vaccines. Write down the date and time of opening of vials. Partially used vials can be used at more than one immunization session for up to four weeks of opening the vial, provided that:

- the vaccine vial monitor (VVM) is in a usable stage
- the vaccine has not crossed its expiry date
- the 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; and
- aseptic technique has been used to withdraw all doses.

To avoid/ minimize immunization error:

✓ Vaccines must only be reconstituted with the diluent supplied by the manufacturer.

Some points to remember for minimising immunization error-related reactions aregiven below.

- Reconstituted vaccine should not be used for beyond 4 hours for BCG and measles containing vaccine, and 2 hours for JE vaccine after reconstitution. The remaining reconstituted vaccines must be discarded at the end of each immunization session and never retained.
- For vaccines that come under the open vial policy, the date and time of opening the vial should be written on the label of the vial (see box).
- 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 are being followed.
- Adequate attention must be given to the possibility of contraindications.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.

Case Studies

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

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

- In 2008–2009, in country B, during a school-based rubella immunization programme, two 14 year-old girls collapsed within a few minutes following immunization. The incidents occurred in two separate places and at different times. Both girls were hospitalized and later died. Investigation revealed that both children had informed the immunization teams about their past history of allergic reactions to some food products, but the immunization teams ignored the history. Also, there were no emergency kits to manage anaphylaxis.

Cause: Immunization error-related reaction. Lack of attention to possible contraindications and precautions to manage anaphylaxis.

Vaccine product-related reaction: anaphylaxis is a known vaccine reaction to rubella vaccine.

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

Cause: Immunization error related reaction: use of insulin instead of DTP.

3.3 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. Fainting is relatively common, particularly in children over 5 years of age. 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.

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.

Immunization anxiety-related reactions should be anticipated in group immunization. Mass hysteria is possible, especially if a vaccinee is seen to faint or have some other reaction. Immunization anxiety can be minimised by giving a clear explanation about the immunization. Stress related to immunization can be reduced through short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient's line of vision and privacy during the procedure. Fainting does not require any management beyond placing the patient in a recumbent position. However, it is important to note that fainting attacks (syncope) can be misdiagnosed as anaphylaxis. Health workers need to differentiate between the two conditions. Careful observation and clinical judgment is necessary (see Annexure 11 on anaphylaxis). However, if by mistake a single dose of adrenaline (intramuscularly) is administered to a vaccinee with just syncope, it does not harm the vaccinee. It is therefore necessary to promote training and awareness for health staff to be able to identify and manage medical emergencies appropriately.

Case Study

In 2004, a school-based mass measles-rubella immunization campaign was conducted for the 12–19 year age group in country D. On the first day, 44 children were hospitalized with either hyperventilation or/and vomiting. Investigation concluded that more than 90% were anxiety reactions and except for two cases all others were discharged from hospital the same day.

Cause: Immunization anxiety-related reactions

3.4 Coincidental events

An event may occur coincidentally with immunization and at times may be falsely attributed to be a result of the administered vaccine. In other words, a chance temporal association, i.e. an event happening after immunization is falsely considered to be caused by immunization. These temporal associations are inevitable, given the large number of vaccine doses administered, especially in a mass campaign.
Vaccines are normally administered early in life when infections and other illnesses are common, including manifestations of an underlying congenital or neurological condition. It is, therefore, possible to encounter many events, including deaths, which can be falsely attributed to vaccine through chance association.

A similar calculation is shown in Table 3.6 below for infant deaths (aged under 1 year) in selected countries for the number of deaths temporally associated with routine DTP or pentavalent vaccine (PVV) immunization. There will be many coincidental deaths in the days, weeks and months after immunization, which are only temporally related to immunization. The actual number of coincidental deaths depends on the population size, infant mortality rate, number of immunization episodes and the 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 also important to 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/very ill will still be immunized.

In general, coincidental events are clearly unrelated, 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 in maintaining confidence in the immunization programme. Availability of information on background rates of reported coincidental events may be helpful in the investigation of an AEFI. If the same or similar events also affected others who did not receive the suspect vaccine(s) in the same age group around the same time, then a coincidental event is more likely. There may also be evidence showing that the event is not related to immunization.

CASE STUDIES

- In response to a severe diphtheria outbreak in country E in 1996, DT vaccine was provided to children in a mass campaign. The death of a seven year-old girl, two to three days following immunization, was reported. The symptoms reported 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 that it was a coincidental event.
- In 2010, six infants died within 48 hours following administration of pentavalent (DTP-HepB-Hib) vaccine in country F. Use of vaccine was temporarily suspended. A high-level investigation was carried out as the deaths had led to a public concern, and health staff was reluctant to use the vaccine. Investigation and assessment revealed that out of six cases, three were confirmed as coincidental. One was due to suffocation and two were due to underlying infections. Among the other three cases, one was diagnosed as anaphylaxis and the other two were inconclusive.
- In 2010, 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 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 national and WHO-accredited laboratories. Causality assessment confirmed the death as coincidental, but the six reported severe local reactions were most likely due to the immunization error-related reactions.

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

Table 3.6. Estimated number of coincidental infant deaths that could be temporally linked to DPT/PVV immunization after immunization in selected countries

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	42	15 000	53	12	2	3 233	746	106
Canada	5	3 88 000	162	37	5	86 864	20 045	2 856
China	13	16 364 000	17 728	4 091	583	3 634 035	8 38 624	1 19 475
India	**47**	**27 098 000**	**1 06 134**	**24 492**	**3489**	**5 810 489**	**1 340 882**	**191 030**
Indonesia	25	4 331 000	9 023	2 082	297	9 50 113	2 19 257	31 237
Iran	21	1 255 000	2 196	507	72	2 76 445	63 795	9 089
Mexico	13	2 195 000	2 378	549	78	4 87 455	1 12 490	16 026
Sudan	57	1 477 000	7 016	1 619	231	3 13 382	72 319	10 303
United Kingdom	4	7 61 00	254	59	8	1 70 540	39 355	5 607

Note: Assumes uniform distribution of deaths and immunization over the time period.
Source: Infant mortality and births from 2011 immunization summary. New York and Geneva: Unicef/WHO; 2013 (http://www.unidef.org/videoaudio/PDFs/EN-immsumm-2013. pdf, accessed 07 December2013).

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*The assumption here is a there-dose schedule for either DTP or PVV, with 90% coverage for each dose.

Summary

Adverse events may occur due to some inherent properties of the vaccine (vaccine product-related reaction), quality defects (vaccine quality defect-related reaction) or immunization error-related reactions.

- At times, the event may be unrelated to immunization but may have a temporal association (coincidental event).
- Immunization anxiety-related reactions resulting from fear or pain of injection are commoner than AEFI resulting from the vaccine itself. In some cases, the cause of the AEFI remains unknown.
- Immunization error-related reactions (previously classified as “programme errors”) are avoidable.
- Antigen/vaccine-specific background rates of vaccine reaction are useful to guide decision-making on vaccine related reactions.
- Minor vaccine reactions are common and do not require special treatment. Rare, serious vaccine reactions need timely treatment by qualified medical personnel.
- Follow open vial policy for prescribed vaccines.

4

Recording and reporting AEFI

4.1 AEFI reporting system

The main service provider for childhood immunization in India is the government sector. The private sector is progressively enhancing its contribution to childhood immunization.

Immunization sessions are conducted in the government-managed centres in primary, secondary and tertiary care institutions on fixed days (that vary in different states) at least once a week. In India, more than two third of the routine immunization services are done in outreach sessions within the public health sector.

Any health-care provider (public or private) who comes across any AEFI has the responsibility of reporting it to the district health authority.

4.1.1 Rural areas

The primary persons responsibile for reporting AEFI are the auxiliary nurse midwife (ANM) at each sub centre that provides health care to a population of 3000 to 5000, the medical officers (MOs) at the primary health centre (PHC) that provides health care to a population of 20 000 to 30 000 and the community health centre (CHC) or block PHC that caters to a population of 80 000–120 000.

4.2.2 Urban areas

AEFI reporting is primarily the responsibility of the health workers and the medical officers of corporations, municipalities and towns. In urban areas, immunization services are provided through urban health posts, maternal and child health centres and district hospitals. Such services are also rendered through dispensaries/facilities of Central Government agencies such as the Central Government Health Services (CGHS), railways, defence services and medical colleges. In addition, reporting should be ensured by paediatricians and clinicians in secondary and tertiary care hospitals as well as the adverse drug reaction (ADR) monitoring centres in the network of the Pharmacovigilance Programme of India (PvPI).

These AEFI guidelines cover all vaccines that are provided through the government or private sector.

4.2 Channels of reporting AEFI

There are two channels of reporting AEFI in the government system:

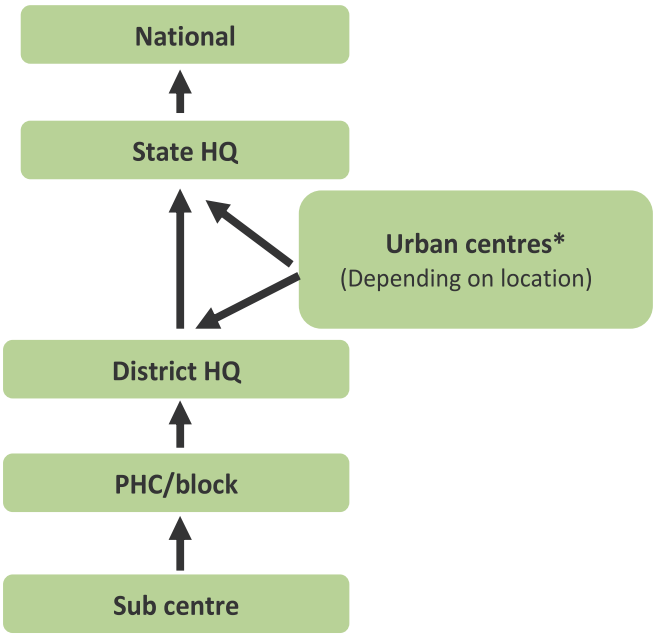
- monthly routine reporting
- immediate, serious and severe AEFI reporting.

4.2.1 Monthly routine reporting

This includes reporting of all serious and minor AEFI from the level of occurrence of the AEFI (health staff at the periphery) up to the national level through monthly progress reports (Figure 4.1). This is done using existing monthly immunization reporting formats such as the ones for National Rural Health Mission (NRHM), Health Management InformationSystem (HMIS), etc. These usually vary from state to state. In the current HMIS system, three main data fields cover all reported AEFI—death, abscess and others. The field "others" should be used to report all AEFI (severe/serious and minor) reported to the health system. It is necessary for the peripheral health staff (usually ANMs) to submit a "nil" monthly report in case no AEFI case is detected from their area during the month. This information is collated and compiled by health staff at the next level (usually at the PHC) under the heading of "any untoward reactions or reportable AEFI" and forwarded to the next level.

For facilitating the process, the PHC staff should collect information on AEFI from ANMs on a weekly basis and document the same in an AEFI register (*see* Annexure 9) to be maintained at the centre. Information of any serious/severe AEFI including "nil" reporting of serious/severe AEFI should be shared with the district immunization officer (DIO) on a weekly basis in the H002 format.

Fig. 4.1. Monthly reporting of AEFI data-flow



*Monthly reports to be sent to the respective district or state HQ though the asst. health officer (EPI)/corporation immunization officer i/c

The current monthly HMIS reporting system captures information on:

- deaths
- injection site abscesses
- others including
  - high grade fever (> 102° F)
  - persistent inconsolable screaming (>3 hours)
  - seizure
  - HHE
  - Other complications (including the cases not listed above such as severe local reaction, brachial neuritis, thrombocytopaenia, lymphadenitis, disseminated BCG infection, osteitis/osteomyelitis

and any untoward incident the vaccinator/ANM/MO think is a result of immunization – both immediate and/or delayed).

4.2.2 Immediate serious AEFI notification (by the first person who identifies the event)

In India, depending on the type of AEFI, the place where the event occurs, its severity and the confidence of the beneficiary in the care provider, serious AEFI are first brought to the notice of the health system by the

- patient directly
- health-care worker who administered the vaccine
- care provider treating the case
- supervising immunization staff
- pharmacy dispensing the vaccine (usually in the private sector)
- local media
- ADR monitoring centres.

It is therefore important that each potential reporter be aware of the process and procedure adopted for reporting serious and severe AEFI.

Immediately after the identification/notification of a serious/severe AEFI, a two-step process is initiated:

- *Step 1*: reporting serious/severe AEFI to the appropriate authority
- *Step2*: district-level investigation of selected reported AEFI.

It is important to initiate case management as a priority over AEFI reporting. Health authorities need to immediately respond to **all** reported AEFI.

All serious/severe AEFI are to be immediately notified by the first person who identifies the event. This person should notify the case to the nearest government PHC/CHC and/or the DIO by the quickest means of communication (telephone, messenger, etc.) All persons involved in reporting AEFI should be aware of the timeline and channels of reporting. All notified AEFI should be documented on a case reporting form (CRF) (*see* Annex1) and submitted to the next level as soon as possible.

Which events should be reported?

It is essential to remember that the health staff should identify and report all severe, serious and minor AEFI. Reportingnon serious of all minor AEFI brought to the notice of the health staff by parents and/or guardians as a concern, such as high fever and minor local reactions, should be done on a monthly basis. Monitoring crude numbers is helpful to record and compare with background rates that could identify product quality defects, immunization errors, or even increased susceptibility to vaccine reactions among the given population.

Reporting minor AEFI

Minor AEFI that are brought to the notice of the health staff as a concern should be reported and documented in a linelist.

AEFI that require prompt reporting and investigation include:

- serious AEFI (death, hospitalization, cluster, disability)
- signals and events associated with a newly-introduced vaccine
- AEFI that may have been caused by an immunization error-related reaction
- significant events of unexplained cause occurring within 30 days after vaccination, and
- events causing significant parental or community concern.

Serious AEFI should be treated as a medical emergency and need to be immediately investigated, managed and reported on standardized AEFI formats. The list of reportable AEFI and the time interval they occur after vaccination are mentioned in Table 4.1.

Table 4.1. List of key serious and severe AEFI for reporting

Reportable AEFI
□ Anaphylactoid reaction (acute hypersensitivity reaction) □ Anaphylaxis □ Persistent inconsolable screaming (more than 3 hours) □ Hypotonic-hyporesponsive episode (HHE) □ Toxic shock syndrome (TSS)
□ Severe local reaction □ Sepsis □ Injection site abscess (bacterial/sterile)
□ Seizures, including febrile seizures □ Encephalopathy
□ Acute flaccid paralysis (AFP) □ Brachial neuritis □ Intussusception □ Thrombocytopaenia
□ Lymphadenitis □ Disseminated BCG infection □ Osteitis /osteomyelitis
□ Death due to any reason other than above (specify)…….. □ Hospitalization due to any reason other than above (specify)……. □ Disability □ Cluster (more than one case report) □ Any other severe and unusual events that are thought by health workers or the public to be related to immunization

Note: *See* Annex 10 for definitions

4.3 Serious/severe AEFI – forms, routing and timelines

The following reporting forms are used to guide AEFI reporting and investigation for any reported AEFI:

1. AEFI CRF
2. AEFI investigation form
   a) Preliminary case investigation form (PCIF)
   b) Final case investigation form (FCIF).

4.3.1 AEFI case reporting form

The CRF captures basic and only minimal information pertaining to the following:

- patient
- event
- vaccine (and diluent)
- reporter.

Purpose

– it provides the most basic information of the event for decision-making at all levels (and is therefore urgent;

– based on the information provided in the CRF, the decision to conduct investigation is taken (and therefore it has to be carefully completed);

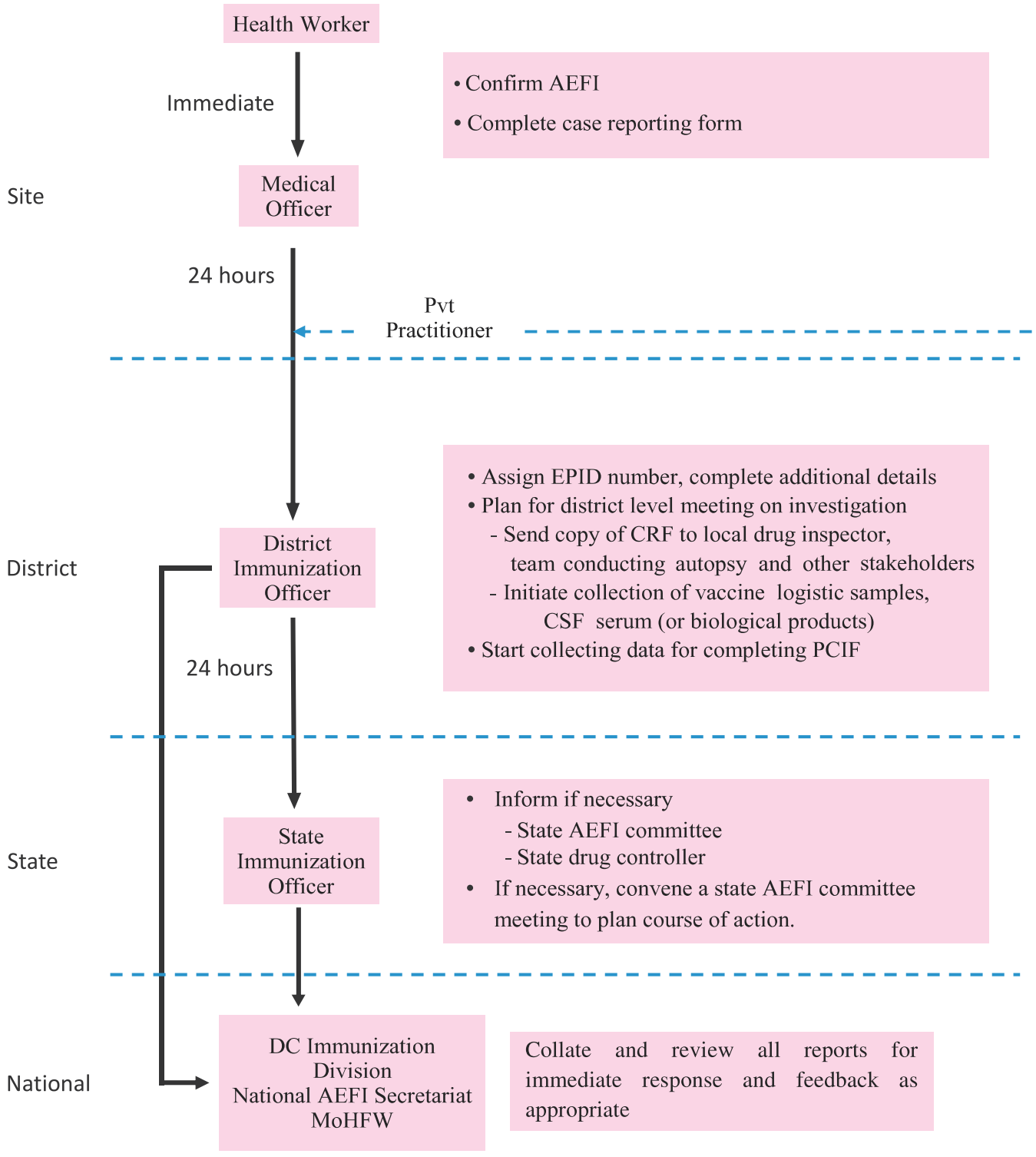
– information on the CRF when collated can identify signals (and therefore sharing this information and doing data analysis is important); and

– CRF is the first reference point for quality assurance and performance of the immunization programme (and therefore can provide information on the health of the system.

Routing and reporting timeline

Routing timeline and actions are given in Figure 4.2.

Fig. 4.2. Case reporting form – routing timeline and actions



Steps in completing CRF

At district level

Preliminary steps and decision making

1. Reporting using the CRF can take place from any level in the government or private sector. The MO enters information in Section A after receipt of information from any source such as a health worker including ANM, AWW, ASHA, ICDS health supervisor, community mobiliser, private practitioner, clinician in tertiary and secondary care hospitals and clinics, informal health practitioners such as rural medical practitioners (RMPs), ADR monitoring centres, etc. followed by a visit to the site.

2. The MO should examine the patient, complete section A of the CRF and submit his reporting form to the DIO within 24 hours of notification of the event to the health system. In case of a reported unexplained death, the MO should make all efforts to ensure a postmortem is conducted at the earliest.

3. The DIO should review the CRF sent by the MO within 48 hours of notification to the health system, and:

   a) complete the details in Section B by providing district-specific information (AEFI EPID number [epidemiological number] and contact details)

   b) decide if detailed investigation is warranted; if yes:

      i. initiate sample collection

      ii. convene a meeting of the district AEFI committee and initiate the process as outlined below.

   c) forward this copy (incorporating Items 3a and 3b) to the state immunization officer, AEFI Secretariat and Deputy Commissioner (DC) of Immunization Division, Ministry of Health and Family Welfare (MoHFW), Government of India (GoI).

Detailed planning following reporting

1. DIO should convene a meeting of the district AEFI committee to determine the need for conducting a time-bound investigation and deciding 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 preliminary and final investigation by the district AEFI team.

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 a postmortem (autopsy) is planned, a copy should be provided to the concerned officer
   - The testing laboratory, along with laboratory request form (LRF) and other documents as outlined in the 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 Chapter 6. The collected samples may be sent only if specified by the district AEFI committee.

Role of State Immunization Officer

On receipt of the completed CRF at the state level, the state immunization officer should decide on the gravity of the AEFI case(s) and take a decision on whether to participate in the state/regional AEFI committee at this stage, or wait for the report of the case investigation form (CIF), or provide support immediately to the district through the state/regional AEFI committee (including the state drug controller).

Role of DC of Immunization Division, MoHFW

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

4.3.2. Preliminary and final case investigation forms

The preliminary and final case investigation forms (PCIF and FCIF) (*see* Annexes 2 and 3) capture 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 the causality.

Contents of the CIF

The CIF includes:

a. Basic details

b. Relevant patient information prior to immunization

c. Details of first examination of severe and serious AEFI cases

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.

Purpose

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

It is important to remember that the CIF is not a "etched in stone" document. Information beyond what is listed in the CIF supported with evidences – including non-conventional sources of information gathered using information technology, are encouraged to obtain the best information possible

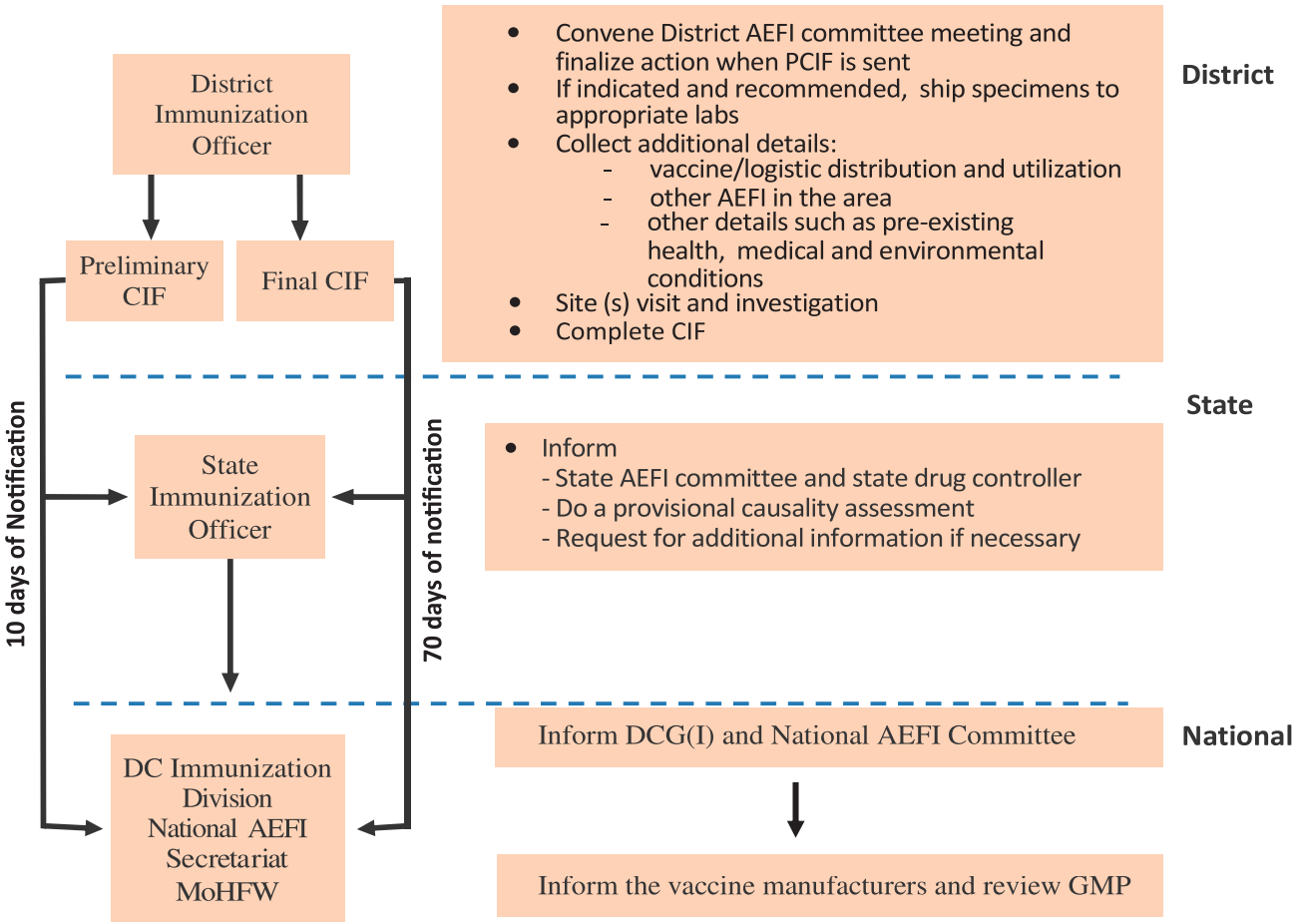
Routing and reporting timeline

– Preliminary CIF (PCIF) – From DIO to the state immunization officer and AEFI Secretariat DC (UIP) MOHFW, GoI as early as possible or within 10 days of case notification. Responsibility is that of the DIO assisted by the district AEFI committee and the area MO/staff.

– Final CIF (FCIF) along with all documents relevant to the case – From DIO to the state immunization officer and AEFI Secretariat DC (UIP), MOHFW, GoI as early as possible or within 70 days of case notification.

The same is shown diagramatically in Figure 4.3.

Figure 4.3: Preliminary and final case investigation form (PCIF and FCIF) – routing timeline and actions



Steps in completing the case investigation form (CIF)

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 PCIF:

    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 with respect to the case(s) as well as to the area.

2. While completing the PCIF, the DIO should ensure that the relevant samples have been sent as part of the investigation including vaccine sample, syringes and injections. In addition, reports of appropriate case investigation samples (if sent) should also be shared for establishing a clinical diagnosis.

3. The DIO should organize the field investigation of the AEFI report with assistance of the district AEFI committee as outlined in the chapter on AEFI investigation. On completing the PCIF he should obtain the committee's endorsement and forward the same to the state immunization officer and National Immunization Division within 10 days of the event.

4. Over the next 60 days after the field visit, the DIO should ensure compilation of all relevant documents including clinical records, hospital records, lab results of urine/blood/CSF, etc./postmortem reports of the case and vaccine and syringe sample tests (if sent to the certified laboratories). A revisit to the case site may be planned if warranted.

5. The district AEFI committee should then summarize the AEFI report in the context of the findings of these tests and attempt to frame a provisional diagnosis of the AEFI case. The DIO should then complete the FCIF with assistance of the district AEFI committee and forward the same to the state immunization officer and National Immunization Division within 70 days of case notification following the district AEFI committee's endorsement.

The 60 day period has been provided to the district to ensure the processing of samples and collection of reports. If the requisite documents are available earlier the same should be sent with the completed FCIF immediately.

It is essential that the DIO should periodically update the state immunization officer and National Immunization Division on the status of the investigation and seek assistance if required.

In urban areas the DIO's counterpart would be the MO in charge of immunization such as the corporation immunization officer, municipal health officer, etc. The role and responsibility of the urban counterparts will be the same as the DIO for detection and responding of the AEFI.

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

State level – role of the 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 supporting documents and decide the 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 for the event, taking into consideration the state's experience with the vaccine(s), and if necessary request for additional information such as laboratory tests, field level information, etc. It is expected that

the causality assessment for a serious case should be conducted by the state AEFI committee within 100 days of case notification.

National level – role of DC (Immunization Division) MoHFW and National AEFI Secretariat

At the national level, the AEFI Secretariat will be responsible for compiling, collating and reviewing all reports of AEFI from the districts. The Secretariat will summarize and update the information and share weekly updates with other vaccine pharmacovigilance stakeholders including the Drug Controller General of India (DCGI) and PvPI. The DC Immunization Division MoHFW, GoI will share the available information of serious and severe AEFI with the DCGI and other senior officers in the MoHFW. The DCGI may inform the drug manufacturers and review GMPs if required.

Maintenance of data and records

District and state level

In addition to a copy of the CRF and CIFs (preliminary and final) and causality assessment reports of all the AEFI reported, the DIO and state immunization officer should maintain a database of all reported AEFI in the form of a line list (*see* Annexes 6 and 7). A quarterly review of data of all serious AEFI should be done by the district and state AEFI committees. 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 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 national level. The monitoring of reported data includes the following information:

- number of AEFI reported
- geographic and temporal distribution of AEFI reported (look for clustering) and epidemiological analysis of the same
- number and type of adverse events reported by antigen, such as injection site abscess, seizures, HHE, etc.)
- geographical distribution of possible programme-related adverse events such as abscesses
- clustering of adverse events according to batch
- timeliness and completeness of reporting

- silent blocks/corporation/districts/states not reporting AEFI data.

Chapter 9 on AEFI Committees gives further details on indicators and analysis for AEFI surveillance.

4.3.3 AEFI reporting by a private health facility/practitioner

The state and district authorities (DIO/CMO/block MO) should ensure that the key private health facilities and focal persons are identified and are sensitized about the AEFI surveillance and reporting system and are encouraged to report AEFI in a timely manner. AEFI reporting is to be encouraged not only for the vaccines supplied by GoI but also for all vaccines being used in the private sector, including new vaccines. An AEFI reported by any private health facility or practitioner 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 reporter. The reporting channels, formats for reporting, investigation and assessment and timelines for vaccines used in the private sector remain the same as mentioned earlier. Professional bodies such as Indian Academy of Pediatrics (IAP) Indian Medical Association (IMA) Indian Public Health Association (IPHA) medical colleges, partner agencies such as WHO/National Polio Surveillance Project (NPSP), UNICEF, USAID, PATH and others should also be encouraged to support AEFI surveillance.

4.3.4 AEFI reporting by ADR monitoring centres

State and district authorities (DIO/CMO/block MO) should ensure that the list of designated ADR monitoring centres and focal coordinators identified by PvPI is available with them and that the coordinators for these centres are aware of the e-mail and contact Nos. of MO/DIO to be reached for reporting an AEFI. These centres must be encouraged to assist the MO/DIO in reporting and investigation of an AEFI. Appreciation for reporting AEFI cases as well as coordination for AEFI investigation and causality assessment should be undertaken by the state and district authorities.

4.4 Steps to encourage reporting

Staff should be encouraged to report AEFI without fear of penalty. Reporting can be enhanced by:

- training
- positive feedback
- ensuring there is enough support available at all levels
- sharing results of the investigation and any corrective action taken.

5

AEFI investigation

5.1 Why reports should be investigated

The ultimate goal of a case investigation is to prepare a clinical diagnosis based on the chronology of medical events, detailed medical history and other evidence such as laboratory investigations. Once a probable diagnosis is available, it will help in finding the cause of the AEFI and undertaking the appropriate response. The investigation should identify any immunization-related errors or vaccine product-related reactions since these are preventable; and if co-incidental events are recognised, then demonstrating these will be important because this will maintain public confidence in the immunization programme.

The objectives of investigating an AEFI case are to:

- Identify the cause of the AEFI
- Confirm/refute the reported diagnosis or establish a clinical diagnosis
- Document the event and its outcome
- Identify the details of vaccine(s) administered and determine the time span between administration of the vaccine and the onset of the event
- Examine the operational aspects of the programme. Even if an event seems to be vaccine product-related/induced (?) or coincidental, immunization-related errors could have triggered or increased its severity.
- Determine whether a reported event was a single incident or one of a cluster. If it is a cluster from the area where the suspected immunizations were given, then determine what vaccines were used.
- Determine whether similar events are occurring in individuals who have not received the same vaccine.

5.2 Which reports should be investigated

The reported AEFI must be investigated if it:

- appears to be a serious event (as defined by WHO) of known or unknown cause
- belongs to a cluster AEFI
- is a suspected immunization error
- appears on the list of events defined for AEFI surveillance
- causes significant parental or public concern
- is a previously unrecognised event associated with any vaccine, especially the newly introduced ones.

Improved reporting can lead to more AEFI reports without actual increase in the rate of vaccine product- or quality-related reaction. The investigator needs to determine if there is a real increase in these reaction rates along with the cause of the increase. For example, a change in vaccine manufacturer or in vaccine lot can lead to a change in reaction rate.

5.3 Steps in investigating AEFI

The following are the steps in an AEFI investigation:

1. Immediate AEFI case notification by the reporter (health worker/clinician/ASHA/AWW/ADR monitoring centre/community/media) in person, via phone, fax or e-mail
2. Case visit for confirmation and reporting in the CRF by the MO to the district
3. Evaluation of completed CRF and decision regarding further investigation by DIO and district AEFI committee
4. Completion of preliminary CIF form, sending laboratory investigations and submission of form with action at the local level by DIO and district AEFI committee
5. Review of lab reports, completion of final CIF and submission by DIO and district AEFI committee to the state AEFI commitee
6. Causality assessment by the state AEFI committee and conclusion of the investigation
7. Review and finalisation of submitted causality assessment by National AEFI Committee
8. Coordination with state and DCGI for action at state and national level.

5.3.1 Initial assessment and information sharing by the health worker

As soon as any trigger event as outlined above is recognized, the health worker should communicate the same to the MO i/c of the block and attempt to treat the event. The health worker should 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 the health worker and shared with the MO on his visit.

A private practitioner should report any AEFI directly to the concerned MO of the nearest government health facility or the district health authority (DIO)

Kindly preserve the used vaccine vials and other logistics under proper cold chain conditions at the nearest cold chain point until further direction from the higher level

5.3.2 Confirming and reporting the AEFI

On receiving information of an AEFI from the area from the health worker or through print or electronic media, the MO should begin an enquiry immediately. He should visit the case, interview the family and collect detailed data about the patient, vaccine/s administered, immunization session in question, vaccine batch and lot numbers used (in the session and in the stored stock of the facility), etc. Based on first-hand information obtained, he should frame a suspected diagnosis, complete section A of the CRF and submit the CRF to the DIO within 24 hours of case notification.

5.3.3 Decision on investigation by the district

On receiving the CRF from the MO, the DIO should first assign an EPID number that should be able to capture information on the state, district, year of occurrence of the AEFI and the serial number. The outline for the code is IND (AEFI) - ST - DIS - YR - NUM (similar to assigning EPID numbers for AFP cases).

- 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 -14 - 001 will be the code of the first AEFI case (001) investigated in Uttar Pradesh(UP) in Ghaziabad district (GZA) in 2014. The DIO should complete section B of the CRF and notify the state and the national programme managers within 48 hours of case notification through fax or e-mail. If the AEFI warrants further assessment, e.g. in case of serious/severe AEFI, he should initiate appropriate actions such as informing the district AEFI committee and initiating action for investigation. A copy of the

CRF should be sent to the local drug inspector, the team conducting the autopsy and other stakeholders; and only if appropriate, the implicated vaccine vial, any other logistic samples, CSF and serum (or other biological products) should be collected and dispatched to appropriate laboratories with a lab request form (*see* Annex 4).

If the case warrants no further investigation, the details of the case should also be included in the monthly routine report and the CRF should be filed for records. Once received at the state and the national levels, relevant information should be added and the CRF filed.

5.3.4 AEFI case investigation

The DIO should lead the case investigation and be supported by members of the district AEFI committee. Background information must be collected for the case such as the pre-vaccination health status, treatment taken and hospitalisation or postmortem details in cases of deaths (if conducted) by the DIO with the support of the concerned MO. Verbal autopsy must be conducted in case of sudden unexplained death following immunization. A district AEFI committee meeting (including the reporting MO) should then be convened to finalise the process of AEFI investigation.

Using the PCIF as a guide, the DIO supported by the MO and AEFI committee members should collect data on the health status of the vaccinee prior to immunization, details of the events that followed vaccination, immunization services, etc. It would also be helpful to obtain the vaccinee 's medical file (or clinical record) to check details about the event from the medical file and other documents, obtain any additional details missing in the CRFand PCIF and identify any other cases that need to be included in the investigation.

Be prepared for...

– Visiting the immunization site, vaccine storage points, residence and locality of the patient (if relevant) and the treatment centre(s).

– Interviewing the patient, parents or guardian, the treating health staff and the staff who provided immunization to collect relevant information.

Possible sources of information in AEFI investigation

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

5.3.5 Steps in investigating AEFIs – aide memoire

1. *Confirm information in report*
2. *Investigate and collect data*
    a. about the patient
    b. about the event
    c. about the suspected vaccine(s)
    d. about other people
3. *Assess the immunization service by*
    a. making enquiries
    b. observing the service in action
4. *Specimen collection when applicable*
    a. from patient
    b. vaccine and logistics
5. *Conclude investigation*

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 investigation form
- Particularly verify the time sequence of vaccination and the reported event
- Obtain any details missing from AEFI reporting/investigation form
- 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 sequence of clinical manifestations and the response to treatment
- Relevant laboratory tests and other investigations (X- ray, ECG) performed, and results
- Details of treatment and outcome.

Step 2c : Investigate and collect data about the *suspected vaccine(s)*

- Shipping conditions from the manufacturer to the last major storage point
- Storage point conditions (refrigerator), documentation and transportation to the vaccination site

- Vaccine handling at the site – cold boxes, condition of ice packs and duration of exposure to ambient temperature
- The condition of VVM
- Time and date of opening the vial
- Date and time of vaccination in the mentioned immunization session, e.g. at the beginning/end of the 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 illness; use a case definition, categorize cases and determine the vaccination status of the affected
- If possible, try to obtain details of other beneficiaries who received the vaccine from
  - the same distribution point
  - the same centre
  - the same vial.

Step 3: Assess the immunization service

Step 3a: Assess the immunization service by making enquiries

- Dosage, person, site and technique
- Vaccine storage, distribution and disposal
- Reconstitution procedure
- Time between reconstituting and administration
- Number/type of immunizations and other medications given, e.g. Vit A at the site on the day
- Staff training.

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

- How vaccines are placed in the cold chain
- If other drugs are stored with vaccines/diluents
- Whether any vials have lost their label
- 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 ambiance of the immunization session (including the interaction of the health worker with beneficiaries) and try to assess if it is child friendly

Step 4: Specimen collection

Step 4a: Specimen collection: *patient* (see details in chapter on sample collection)

Event	Specimen from the patient
Severe local reaction	Blood
Abscess	Swab blood
Lymphadenitis	Blood
CNS symptoms with no paralysis	Cerebrospinal fluid, blood
CNS symptoms with paralysis	Stool
Anaphylaxis	Blood
Toxic shock syndrome	Blood
Death	Postmortem tissue specimen

Step 4b: Specimen collection: *vaccine*

- Evaluating the vaccine
- Testing vaccine quality rarely needed
- May be part of regulatory protocols
- Only on clear suspicion, not as routine, and never before a working hypothesis has been formulated
- Following tests may confirm/rule out suspected 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).

Step 5: Concluding investigation

- Review epidemiological, clinical and laboratory findings
- Formulate hypothesis on the likely/possible cause(s) of the event
- Test hypothesis, if possible
- Reach a provisional conclusion on the cause
- Complete AEFI investigation form.

The DIO should ensure that the preliminary investigation of the case is carried out and documents submitted to state immunization officer and AEFI Secretariat, DC of Immunization Division, GoI within 10 days of case notification by the health worker (within 7 days of CRF submission).

Over the next few days, the DIO should compile all documents relevant to the case. A district AEFI committee meeting should be convened by the DIO where all these documents should be reviewed and an attempt made to establish the diagnosis of the case. A revisit to the case may be planned if warranted.

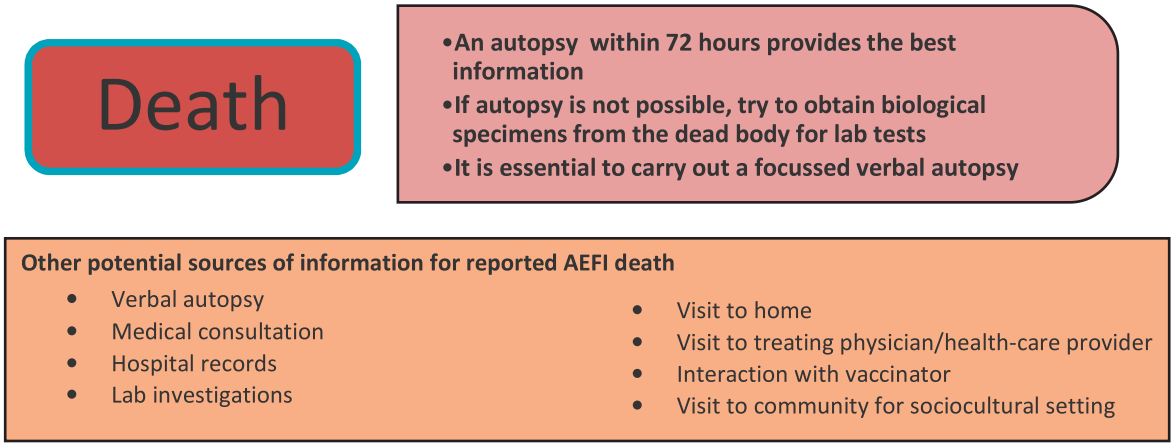
The completed FCIF with all relevant documents should be sent within 70 days of notification to the state immunization officer and AEFI Secretariat, DC of Immunization Division, GoI.

Copies of the following documents are expected to be sent along with the CIFs, depending on their availability:

- Hospital records
- Result of any pathology/microbiology test (blood, CSG, urine)
- Doctor's prescription/treatment record for this AEFI
- Doctor's prescription/treatment record for other illnesses
- Report of laboratory test of vaccine/diluent (if sent for testing)
- Result of laboratory result of syringes/other drugs
- In case of death –
    - Completed verbal autopsy form (in cases of sudden unexplained death)
    - Autopsy performa/postmortem report (if conducted)
- Any other relevant document.

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. Report of an AEFI death should be immediately notified to all administrative levels, including the National AEFI Secretariat at the Immunization Division, MoHFW. 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. All information of the event should be provided to the investigation team.



5.3.7 Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. The exact nature of the relationship between the adverse events such as duration of "time" or proximity of "place" will differ by the nature of the events and the circumstances under 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 investigation begins by establishing the case definition and identifying all cases that meet the case definition. The DIO should then take two actions:

– 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, etc.)
  - information regarding immunization practices of health workers for preparation, handling, reconstitution and administration of vaccines.

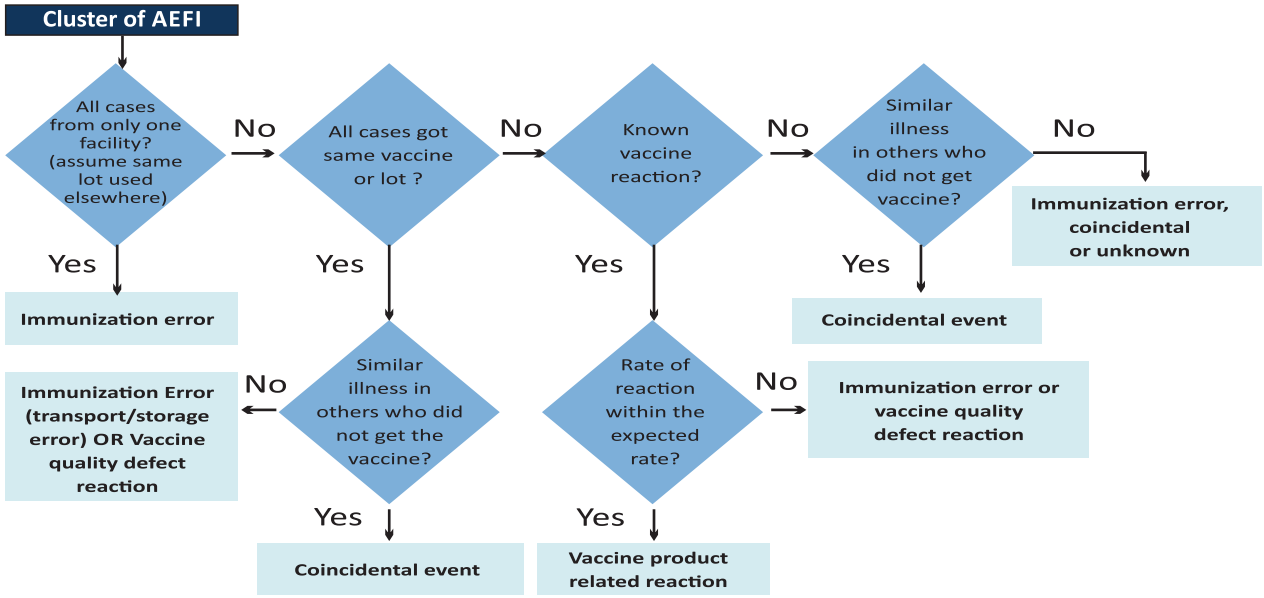
– Identify any common exposures among the cases such as:

  - all data on vaccine(s) used (name, lot number, etc.)
  - data on other people in the area (also non-exposed).

Cause-specific AEFI	Cluster characteristics
Vaccine reaction (product-related or quality defect-related)	If all cases received the same vaccine or lot and there are no similar cases in the community 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 include people from the same area in the same age group but were not vaccinated
Immunization anxiety-related reaction	Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programmes targeting adolescent girls

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 of a vaccine quality defect as well as whether an immunization error 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.

Fig. 5.1. Identifying causes of an AEFI cluster



Case studies (examples)

- In 2006, in a state A, four separate AEFI clusters of "collapse" occurred within 5 to 20 minutes following immunization with measles vaccine. All 14 cases presented with hypotonia; 11 became pale; seven cases had cyanosis, dyspnoea and increased saliva secretion; three cases had difficulty in breathing and eight cases died; others recovered in less than one hour. In two of the sessions, vials that contained muscle relaxants were found stored with vials containing diluent, and of the same size and shape; labels on a number of vials recovered could not be read. Investigations revealed use of a muscle relaxant.

  Cause: Use of muscle relaxant instead of diluent.

- In 1999, in state B, 21 infants died out of 70 infants supposedly given DPT vaccine. Insulin was stored in similar-looking vials in the same refrigerator as DPT vaccine.

Cause: Use of insulin instead of DPT.

- In 2008 in state C, three infants died after administration of measles vaccine. Symptoms that developed within one and a half hours following immunization were fever, rash, vomiting and diarrhoea—described by the attending health worker as "toxic shock syndrome". Reconstituted vaccine was routinely kept until it was used, and as AD syringes were not available the vaccinator used the glass syringes which were never sterilized, but washed with ordinary water and wiped with cotton wool. No testing could be done.

Cause: Non-sterile injection (contaminated reconstituted vaccine).

- In 2009, in State D, four children died and a fifth was hospitalized after receiving measles vaccine from the same vial. The infants died within minutes after receiving the vaccine. Before death the presenting signs and symptoms were high fever, frothing, vomiting, respiratory distress, cyanosis, rolling over of eyes and unconsciousness. The investigators found out the vaccinator had used some other drug instead of the diluent.

Cause: Use of some other drug instead of diluent.

Summary

- Investigation should be timely, comprehensive and methodical
- Laboratory investigation(s) are important, but should not be routinely done for vaccine and other logistics. To be conducted only if indicated and necessary
- It is recommended to secure investigational items (vaccine, syringes, blood, etc). in proper conditions, in case they are needed later for laboratory investigations
- Autopsy investigations are often essential to exclude any coincidential causes of an AEFI death.

6

Investigation of reported sudden unexplained deaths following vaccination

The sudden and unexpected death of an individual, especially that of a child, is one of the most traumatic and sad events that can happen to a parent/family. Investigation of suspected unexplained deaths following immunization is an issue of great importance with regard to the immunization programme, as the proper causality assessment would enable differentiation of vaccine- related deaths from deaths due to other causes.

It is important to understand that in the vast majority of reported sudden unexplained infant deaths, it is possible that the death may be due to natural causes. In a small number of cases, death may be as a result of negligence or a deliberate act. It is important to accurately identify these cases so that in future, children can be protected.

There are likely to be a number of factors contributing to sudden and unexpected death. It is important to identify these factors by detailed investigation of the history, circumstances of death, medical examination, postmortem report and liaison with professionals involved with the family. Many causes of death from genetic, metabolic or cardiac disorders that were previously unknown have recently come to light.

In order to rule out causes of death such as trauma, crib-related deaths including falling from the crib or cot, parents accidentally rolling over the baby during sleep, or other reasons for unexplained deaths, the field worker must examine the site of death. If the child has not been moved, a photograph may be taken immediately for the purpose of documentation.

Investigations of AEFI deaths are multidisciplinary and final collation and interpretation of results would require corroboration with a detailed history that may be forgotten unless documented at the time of the incident.

Specialised documents have been developed to improve the investigation of unexplained AEFI deaths.

6.1 Verbal autopsy form

The verbal autopsy form has been designed based on the WHO and Centers for Disease Control and Prevention (CDC) sudden unexplained infant death investigation (SUIDI) form , whereas the guidance on conducting autopsy has been designed by a committee of leading experts in the field of immunology. These are to be filled by the investigating MO and followed by the DIO when investigating any reports of AEFI deaths where inadequate information is available regarding the terminal event, such as brought dead to health facility, home death, insufficient medical records regarding the event, death in a case that was not hospitalized or if clinical diagnosis is not possible based on available evidence.

Some of the salient details that are recorded in the verbal autopsy form include:

- **Documentation of general details**

  All details related to the deceased must be available.

  - Name
  - Date of birth/age
  - Gender
  - Name of the parents
  - Name of the care-giver (if in foster homes), nannies employed by the parents, grandparents and other family members if living in the same house, etc.
  - Address
  - Time of death
  - Location of death (includes hospital)
  - Name of the MO
  - Name of person who first found the child dead (including nurse/health worker)
  - Contact details of those who could give details regarding the case.

– **Documentation of vaccination details**

  - Immunization details
  - Nature of last vaccination given
  - Route of vaccination
  - Number of children vaccinated by the same vial in case of multiple dose vial. These children must be examined for excluding an AEFI
  - 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 observed or reported during current or past immunization.

– **Overview of the incident**

A history related to the incident must be provided—who was involved, what happened, where, when, why and how the incident occurred. The investigation team must visit the site of incident to document and obtain more history. A detailed history and documentation which includes a temporal description of events starting from 24 hours prior to and up to the occurrence of the event and declaration of death by a competent person is essential to understand cause of death. Hence a host of other common causes need to be excluded. Further, the death may be unrelated to vaccination and this needs a proper clinical–pathological correlation.

6.2 Guidance on conducting autopsy

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 an AEFI death. It may be especially mandatory in those instances when there have been previous reports of similar deaths that went uninvestigated and when public at large are worried about such deaths and are likely to lose or have lost faith in the vaccination programme.

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 postmortem artifacts 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 is submitted to the team (autopsy surgeon/pathologist/forensic specialist) conducting the autopsy.

Please refer to Annexure 17 for details on autopsy in an AEFI case resulting in death

7

Specimen collection and handling for AEFI

Only the appropriate specimen in the correct quantity required for the investigation should be collected. Laboratory specimens should be accompanied by clear supporting documents (LRF, CRF, CIF and other relevant documents), reasons for specimen collection and any specific additional request for information by the investigators. Activities and responsibilities for specimen collection following an AEFI are given in Table 7.1.

Table 7.1: Activities and responsibilities for specimen collection following an AEFI

	Activity	Responsibility
1	Decision to collect sample (samples should be collected as soon as possible and sent only if the district AEFI committee decides)	District AEFI committee that includes the local drug inspector. If required consult state AEFI committee
2	Decision to temporarily suspend the use of implicated batch of the vaccine/diluent/logistics	MoHFW, GoI The local drug authority representative after discussion with the AEFI committee
3	Collection and sending of samples	Drug inspector and DIO
4	Decision on type of samples that need to be collected	Based on recommendations of the district AEFI committee The drug inspector may also collect additional samples he considers appropriate
5	Packaging and cold chain of samples	Drug inspector and DIO
6	Sealing of specimen using official lac seal	Preferably by drug inspector; in case the drug inspector's seal is not available, then by using the CMO's seal

7	Transportation of samples to laboratories	Preferably DIO and/or drug inspector
8	Laboratory for sending specimen	Identified laboratories as described in this chapter
9	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 Part C (Immunization) of NRHM PIP (under the provision for "state specific activities") after due approval by competent authority at block/district/state level. All expenses towards testing of vaccines in CDL Kasauli and Kolkata will be borne by the respective laboratories. NIV Pune and NIV Gorakhpur will bear the expenses related to testing of samples for adverse events occurring following JE vaccination
10	Reporting of laboratory results/reports	The laboratory as a rule will forward a copy of the report to CDSCO, DC 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, fax number and e-mail address) mentioned in the LRF
11	Feedback of laboratory results	DIO to share with – District cold chain officer – Drug inspector – Block MO reporting the case – Private health facility reporting the case

It is essential that testing be conducted for biological samples from the patients; if indicated, testing of vaccines, diluents and logistics are also performed. Laboratory testing of samples is not mandatory following AEFI, particularly if the cause is evident, such as a coincidental event or an immunization-related error. However, laboratory testing is at times required to confirm or rule out the suspected cause.

The laboratories where tests are performed are outlined below.

– **For biological samples**

- Histopathology, body fluids, etc. at laboratories identified and approved by the district/state AEFI committees
- Autopsy specimens at approved and accredited state forensic laboratories.

– **As per the Central Drug Standard Control Organization (CDSCO)**

- Vaccines and diluents for sterility and chemical composition at Central Drugs Laboratory (CDL) Kasauli
- Syringes and needles for sterility at CDL Kolkata.

7.1 Testing of biological specimens

The district AEFI committee should identify govt and reliable private laboratories for testing of biological products such as blood, cerebrospinal fluid (CSF), urine, etc. However, in case of adverse events occurring following JE vaccination, the CSF and blood samples should be sent to National Institute of Virology at Pune or Gorakhpur after proper labelling and packing along with LRF and CRF. CIF and other relevant documents may be included if requested.

NIV Pune – contact details
The Director, National Institute of Virology (JE Group)
Sus road campus, Pashan, Pune 411021, Maharasthra
Mail: nivicl@pn3.vsnl.net.in, acm1750@rediffmail.com
Tel : 020-25880982, 020-26127301, 020-26006290;
Fax : 020-25883595, 020-26122669, 020-26126399

7.1.1 Biological specimens from AEFI cases

It is difficult to generalize what specimens will be required in a given situation as it will depend on the symptoms and signs of the patient and the clinical decisions made by the doctor in charge of the case. Table 7.2 gives a general outline of some of the specimens that could be collected. The list is not exhaustive.

Table 7.2: Biological specimens to be collected for testing following AEFI

Event	Specimen from the patient
Severe local reaction Abscess Lymphadenitis	Swab, blood
CNS adverse events CNS symptoms, no paralysis CNS Symptoms, with paralysis	Cerebrospinal fluid (CSF), blood, Stool*
Others Anaphylaxis Toxic shock syndrome Death	Blood, blood culture, postmortem tissue specimen (as directed by physician) Urine

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

7.1.2 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 postmortem artifacts 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 additional specific information to the autopsy team will help them in looking for any underlying disease/pathologies in the deceased which may have been the cause of death or contributed to the cause of death.

Samples for both histopathological and toxicological examination should be sent to approved and accredited govt reference laboratories through investigating police agencies. The samples should be collected and transported to forensic laboratories as early as possible to avoid loss of biological samples due to decomposition. All samples should be labelled with the name and EPID number. The sample should be sent along with the autopsy report/form, documents requesting the examination and investigation and the conclusions from the autopsy which should list the cause of death utilizing International Classification of Disease (ICD-10) and, if possible, the causative agents/drugs. The important aspects to be considered when conducting autopsies are outlined in Annex 15.

7.2 Testing of vaccine/diluents at CDL Kasauli

On the receipt of adequate samples with proper and complete documentation, CDL at the Central Research Institute, Kasauli tests vaccines and diluents for physical aspects, sterility, abnormal toxicity and biochemical identity. Tests for potency are not applicable in AEFI cases, since potency is related to efficacy rather than safety of vaccines. Laboratory tests are performed and results dispatched to the sender in approximately 30–45 days.

Laboratory testing for implicated vaccines/diluents/logistics should be requested only on a clear suspicion 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 an 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.

- First collect each vaccine/diluent as described in Table 7.3. Prepare four sealed sets with equal quantity in each and
    - ➢ send one set to CDL Kasauli
    - ➢ retain one set at the site of collection (PHC/CHC or district HQ)
    - ➢ 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 numbers outlined in Table 7.3 are not available at the last vaccine storage point.
- It is important that the quantity required by CDL Kasauli must not be compromised.

Table 7.3: 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/ampoules	Unused diluent vials/ampoules	Unused vaccine vials/ampoules (one fourth of total samples collected)	Unused diluent vials/ampoules (one fourth 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
Oral polio vaccine	20 doses x 40 vials	NA	20 doses x 10 vials	NA
Measles/MMR	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 and hepatitis vaccines	01 dose x 120 vials *or* 05 doses x 60 vials *or* 10 doses x 40 vials	120 diluents 60 diluents 40 diluents	01 dose x 30 vials *or* 05 doses x 15 vials *or* 10 doses x 10 vials	30 diluents 15 diluents 10 diluents

7.2.2 Packing of samples

- Separate plastic zipper bags should be used for packing different vaccines and diluents.
- The name, age, date of collection, AEFI/ EPID number and point of collection of vaccines/diluents should be mentioned only 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 bigger zipper bag should be placed in a cardboard box, tied with a string from all sides and an official lac seal affixed by the drug inspector (Figures 7.1 and 7.2). The CMO's official lac seal may be used if the official lac seal of the drug inspector is unavailable.

Fig. 7.1 Sample seal

Fig. 7.2 Sample seal

7.2.3 Documentation and transportation of sample to laboratory

- The completed LRF (Annex 4) 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 the 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 freeze-dried vaccines (BCG, measles and JE) should be accompanied by their respective diluents.
- 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 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 a courier service that has experience in handling biological products and can also guarantee delivery up to CDL Kasauli within the stipulated time under the stipulated conditions.

Example of vaccine/diluent collection

An AEFI occurred in district M following use of a 5-dose vial of measles vaccine at a session site. The district AEFI committee reviewed the case and decided to collect the implicated batch of measles vaccine and diluent for testing in CDL Kasauli.

As per guidelines (Table 7.3), the team comprising the DIO and drug inspector planned to collect 60 vials of measles vaccine and 60 ampoules of measles 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 measles 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 session site and PHC.

The next step was to collect 60 measles diluents. They could only collect 45 diluents of the implicated batch from PHC; another 15 diluents were collected from the district vaccine store. The total quantity required, i.e. 60 diluents was now complete. The sample was packed in zipper bags and labelled accordingly.

The zipped and labelled bunches of 15 vaccines and 15 diluents were placed in cardboard cartons, sealed with the drug inspector's official lac seal and 4 sets were made.

They sent one set containing 5 vaccine vials (unused) and 15 diluents (unused) under cold chain for testing to CDL Kasauli (Table 7.3) along with a LRF, CRF and CIF.
The rest of the sets was packed and retained at different levels as per guidelines mentioned above.

Tests done on opened used/partially used vials at CDL Kasauli

Used (opened) vials are technically not required by 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 are being sent for testing.
The opened vials are usually not tested because of 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.

Address for shipment of vaccines and diluents
Head, Central Drugs Laboratory, Central Research Institute, Kasauli - 173 204, Himachal Pradesh.
e-mail: nclkasauli@bsnl.in; Phone: 0179-2272046, 2272060 ; Fax: 0179-2272049, 2272016

The district is still advised to preserve the open vials in adequate cold chain and wait for directions from the state/centre before discarding them.

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 pack is then put in the vaccine carrier or thermocol box with ice packs. (Dry ice may be used for OPV samples but **never** for freeze sensitive vaccines.)
8. The address of 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 Figures 7.3 and 7.4.
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.

Fig. 7.3 Incorrect labelling

Fig. 7.4 Incorrect labelling

7.3 Testing of syringes, needles and vitamin A samples at CDL Kolkata

CDL Kolkata is the identified laboratory where implicated sample 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 a decision by the district/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 in approximately 60 days after 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 (vaccine) as per the Drugs and Cosmetics Rules, 1945 as amended and transfer of sealed samples to CDL Kolkata. The samples 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 has to be sent for testing, one set retained at the point of collection and two sets retained with the drug inspector (Table 7.4). The samples can be sent through a reliable courier or postal services. Cold chain is **not** required.

Table 7.4 Quantity of unused syringes/needles and Vit A to be collected for testing

Sample	Unused quantity of implicated batch
AD syringes	4 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 • 2 sets of 50 pieces each (total 100) to be retained by drug inspector(local drug authority)
Reconstitution syringes	4 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 • 2 sets of 50 pieces each (total 100) to be retained by drug inspector(local drug authority)
Vitamin A	4 Sets of two 100 ml bottles (total 8 bottles) • 2 bottles for CDL Kolkata • 2 bottles to be retained at the source of collection • 4 bottles to be retained by drug inspector(local drug authority)

7.3.2 Packing, documentation and shipment

- The used samples (auto-disable [AD] syringes/reconstitution/disposable/VitA) 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 cardboard box, tied with string from all sides and 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 – 6000016
e-mail: cdlkol@gmail.com Phone: 033-22299541 Fax: 033-222 99380, 033-222 98336.

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

- In case Vitamin A is being sent for testing, the used bottle if available can also be sent along with the unused sealed bottles of Vitamin A with quality packing 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 MO in charge. Documents requested by the police/other investigating agencies should be shared as attested copies.*

8

Causality assessment of AEFI

Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood of the event having been caused by the vaccine/s received. This does not necessarily establish whether or not a definite relationship exists, but generally 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. Vaccine recipients want to know whether what they have experienced was due to the vaccine. They may believe that because one event followed another, it was causal. It can be difficult to explain that such might not have been the case. Causality assessment may provide a more descriptive explanation that may reassure the vaccinee and lead to better management of the event that ultimately helps the vaccinee. In essence, whether an AEFI might be attributable or not to the vaccine or the vaccination determines what steps need to be taken to address the event.

Causality assessment is important for:

- identification of vaccine-related problems;
- identification of immunization error-related problems;
- excluding coincidental events;
- detection of signals for potential for follow-up testing of hypothesis and research; and
- validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

The quality of the causality assessment depends on three factors:

1. The performance of the AEFI reporting system in terms of responsiveness and effectiveness—the quality of case reporting and follow-up investigation
2. Availability of adequate medical and laboratory services for the investigation and follow up of cases, and access to background information on population and 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, an adequate causality assessment might not be performed; or the AEFI may be deemed unclassifiable or inaccessible due to lack of information. On the other hand, even with complete information the AEFI may 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 the 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 will usually not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

8.1 Who should conduct the causality assessment

The state immunization officer should ensure that the causality assessment is conducted by the state AEFI committee within a month of receipt of the AEFI case investigation form and other documents at the state. A copy of completed causality assessment form along with completed relevant documents should be sent to DC Immunization. The final report should include the diagnosis, type of adverse event and the key remarks/inputs of the district and state AEFI committees.

8.2 Criteria for causality in the causality assessment process

The 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 seven are the most relevant to the question "Can the given vaccine cause a particular event?". The first criterion is essential.

i. **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.

ii. **Biological plausibility.** Biological plausibility may provide support for or against vaccine causality. In other words, the association should be compatible with existing theory and knowledge related to how the vaccine works.

iii. **Strength of the association.** The association should meet statistical significance to demonstrate that it was not simply a chance occurrence. The stronger the association, the more likely that the relation is causally associated.

iv. **Consistency of the association.** The association is consistent when results are replicated in studies in different settings among different populations using different methods.

v. **Specificity.** The vaccine is the only cause of the event that can be shown.

vi. **Definitive proof that the vaccine caused the event.** Clinical or laboratory proof that the vaccine caused the event. It is most often found in live attenuated vaccines.

vii. **Consideration of alternate explanations.** In doing causality assessment, all reasonable alternative aetiological explanations need to be considered.

viii. **Prior evidence that the vaccine in question could cause a similar event.** We must look for prior evidence in the published literature or during pre-licensure studies that a particular clinical event is associated with the vaccine given. The concept of "re-challenge" which is more commonly used in drug causality has also been helpful for certain vaccine-event considerations, e.g. Guillian-Barre Syndrome or GBS occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine. However, re-challenge should not be done as a planned procedure to "prove" causality of the event by the vaccine.

8.3 Case selection for AEFI causality assessment

All cases being investigated by the districts should be assessed for causality by the state AEFI committee. It is therefore recommended that causality assessment be done for the following:

- Serious AEFI as per the regulatory definition of serious, i.e. events which are life-threatening or leading to death, hospitalization, significant disability or clusters, where it is important to evaluate whether a vaccine could have been responsible for the event
- AEFI that may have been caused by immunization error, e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, etc.
- Significant events of unexplained cause occurring within 30 days after a vaccination (and not listed in the product label)
- Events that are causing significant parental or community concern and where a formal case assessment can provide a detailed, more reassuring explanation to the parents and/or community, e.g. HHE, febrile seizures
- Signals generated as a result of an unusual individual case or a cluster case that will then warrant further analysis and other investigations.

8.4 Steps to be taken before starting a causality assessment

There are three prerequisites that every AEFI report should fulfil before causality assessment:

1. The AEFI case investigation should have been completed. Premature assessments with inadequate information could mislead the classification of the event.
2. All details of the case should be available at the time of assessment. They should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.
3. There must be a "diagnosis" (see below) for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question. In other words, it should be clearly understood which vaccine is being associated with what specific event that was reported.

8.5 Causality assessment method

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 for causality assessment as outlined below.

Step 2: **Checklist**: to systematically review the relevant and available information to address possible causal aspects of the AEFI (*see* Annex 1).

Step 3: **Algorithm**: to obtain a direction as to the causality with the information gathered in the checklist.

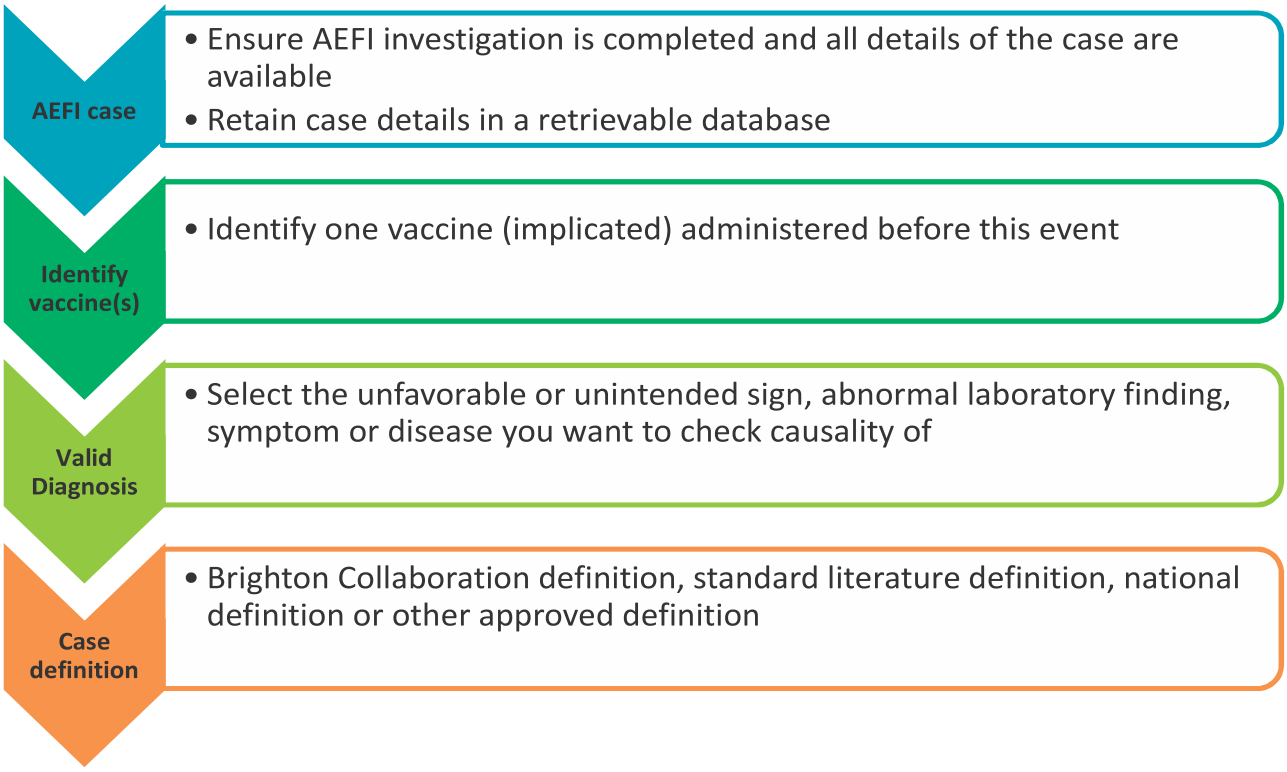
Step 4: **Classification**: to categorize the AEFI's association to the vaccine/vaccination based on the direction determined in the algorithm.

8.5.1 Eligibility

This may be self-evident, but to proceed with causality assessment it is necessary to first confirm that the vaccine was administered before the event occurred. This can be ascertained by eliciting a careful history with the relevant stakeholders to ascertain the timing of vaccination with the onset of any signs and/or symptoms related to the event being assessed. It is also essential to be clear on the "diagnosis" of the reported AEFI. The valid diagnosis could be a clinical sign, symptom, abnormal laboratory finding, or disease with clear details as to onset. The diagnosis should also 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. However, if this is not possible, case definitions can be adapted from the standard medical literature, national guidelines or local clinical practice. 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 or clear definition of what event is being assessed for causality against the given vaccination. Figure 8.1 illustrates the above.

Another important point is that while the revised process envisages the causality assessment of an individual AEFI case with a particular vaccine, in the event of multiple vaccines being given simultaneously, a causality assessment may have to be conducted taking into account each vaccine separately.

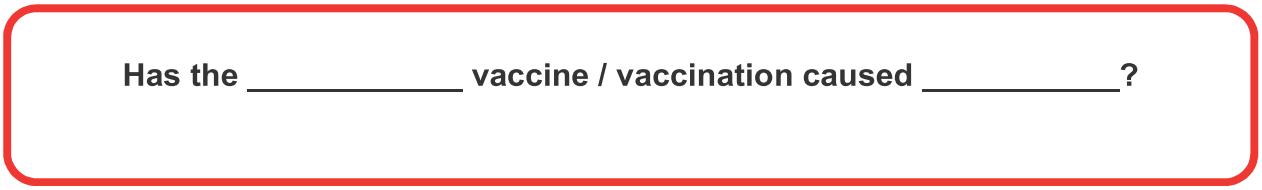
Fig. 8.1. Causality assessment: eligibility



It is important that if an AEFI is reported and appears to not meet the eligibility criteria because of inadequate information, attempts should be made to collect the additional information required in order to ensure that the case can be properly assessed for eligibility. Additionally, all cases reported (including those deemed or eventually deemed as ineligible cases) should be stored in a repository (preferably electronic) so that they can be accessed should additional information become available through reports of similar cases, new evidence in the literature, or through periodic database analysis.

On successful completion of this stage, the reviewers should define the "causality question" (Figure 8.2). It is recommended to write the name of one vaccine at a time in this question. Write the valid diagnosis in the next space.

Fig. 8.2. Causality question



Examples of causality questions

- "Has the vaccine A caused hepatomegaly?" (An example of an unfavourable or unintended sign)
- "Has the vaccine B caused thrombocytopenia?" (An example of a laboratory finding)
- "Has the patient complained that the vaccine C caused itching and redness?" (An example of a symptom)
- "Has the vaccine D caused meningitis?" (An example of a disease).
- ***"Death" is not a valid diagnosis. The pre-existing conditions or the circumstances leading to death should never be mentioned as a valid diagnosis***

8.5.2 Checklist

The checklist contains elements to guide the assessor or committee of reviewers to collate the evidence for case review. It is designed to assemble information on patient–immunization–AEFI relationships in the following key areas:

1. Is there evidence of other causes?
2. Is there a known association with the vaccine/vaccination in the medical literature, and if so, did the event being assessed occur within an appropriate time window?
3. With the vaccine product, or as an immunization error, or immunization-related anxiety
   - is there any strong evidence against a causal association?
   - are there other qualifying factors for classification—background rate of the event, present and past health condition, potential risk factors, medication, biological plausibility, etc.?

The checklist process is illustrated in Table 8.1.

Table 8.1: The causality assessment checklist

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination or laboratory tests on the patient confirm another cause?	☐ ☐ ☐ ☐	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐ ☐ ☐ ☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐ ☐ ☐ ☐	
Immunization error		
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.?	☐ ☐ ☐ ☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐ ☐ ☐ ☐	
Was the vaccine's physical condition, e.g. colour, turbidity, presence of foreign substances, etc. abnormal at the time of administration?	☐ ☐ ☐ ☐	
Was there an error in vaccine constitution/preparation by the vaccinator, e.g. wrong product, wrong diluent, improper mixing, improper syringe filling, etc.?	☐ ☐ ☐ ☐	
Was there an error in vaccine handling, e.g. a break in the cold chain during transport, storage and/or immunization session, etc.?	☐ ☐ ☐ ☐	
Was the vaccine administered incorrectly, e.g. wrong dose, site or route of administration, wrong needle size, etc.?	☐ ☐ ☐ ☐	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization, e.g. vasovagal, hyperventilation or stress-related disorder?	☐ ☐ ☐ ☐	
Time **– if "yes" to any question in II, was the event within the time window of increased risk?**		
Did the event occur within an appropriate time window after vaccine administration?	☐ ☐ ☐ ☐	

III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	☐☐☐☐	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	☐☐☐☐	
Could the event be a manifestation of another health condition?	☐☐☐☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐☐☐☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐☐☐☐	
Was there acute illness prior to the event?	☐☐☐☐	
Did the event occur in the past independently of vaccination?	☐☐☐☐	
Was the patient taking any medication prior to vaccination?	☐☐☐☐	
Is there a biological plausibility that the vaccine could cause the event?	☐☐☐☐	

Y: Yes; N: No; UK: Unknown; NA: Not applicable.

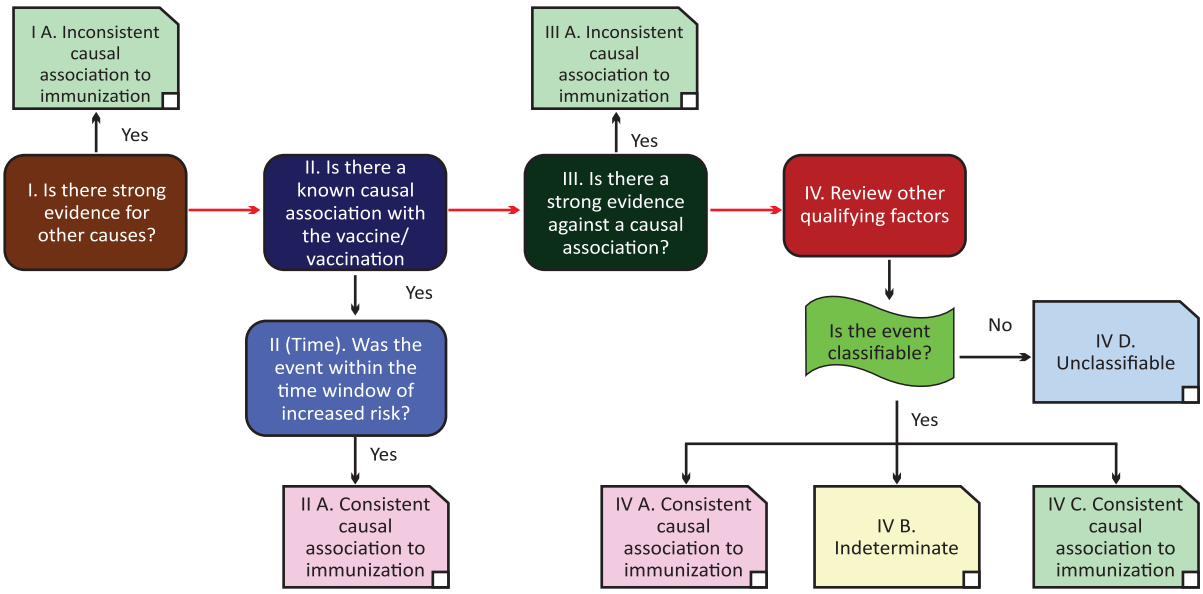
8.5.3 Algorithm

Once the checklist is completed, the AEFI case is ready to be applied to the algorithm. The algorithm aims to be a roadmap for the decision-making of the 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, an indeterminate outcome or is unclassifiable.

The algorithm allows the reviewers to focus logically and document their observations to

reach appropriate conclusions. “Yes” responses in the checklist should have corresponding conclusions in the algorithm. This is illustrated in Figure 8.3.

Fig. 8.3. Causality assessment algorithm



: Mandatory path

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; red if it is consistent with a causal association to immunization; yellow if it is indeterminate; and blue if the event is unclassifiable.

Summarizing the responses in the checklist adjacent to the corresponding conclusion or as a summary note at this point will enable the reviewers to have a transparent "dashboard view" of their conclusions and the logic for arriving at them.

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 why classification was not possible and all attempts should be made to obtain the necessary supporting evidence for classification.

8.5.4 Classification

The final classification is based on adequate information being available for the case as mentioned above. After stepping through the algorithm, a case can thus be classified as follows:

A. Consistent causal association to immunization

A1. Vaccine product-related reaction. Example – extensive limb swelling following DTP vaccination; or
A2. Vaccine quality defect-related reaction. Example – failure by the manufacturer to completely inactivate a lot of inactivated polio leads to cases of paralytic polio; or

A3. Immunization error-related reaction. Example – transmission of infection by contaminated multidose vial; or
A4. Immunization anxiety-related reaction. Example – vasovagal syncope in an adolescent following or during vaccination.

B. Indeterminate

B1. Temporal relationship is consistent but there is insufficient definitive evidence of the vaccine having caused the event (maybe a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation. Example – irritable bowel syndrome after TT vaccine (hypothetical and unproved so far).

B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization. Example – thrombocytopenia after MMR vaccine in a dengue endemic area.

C. Inconsistent causal association to immunization (coincidental)

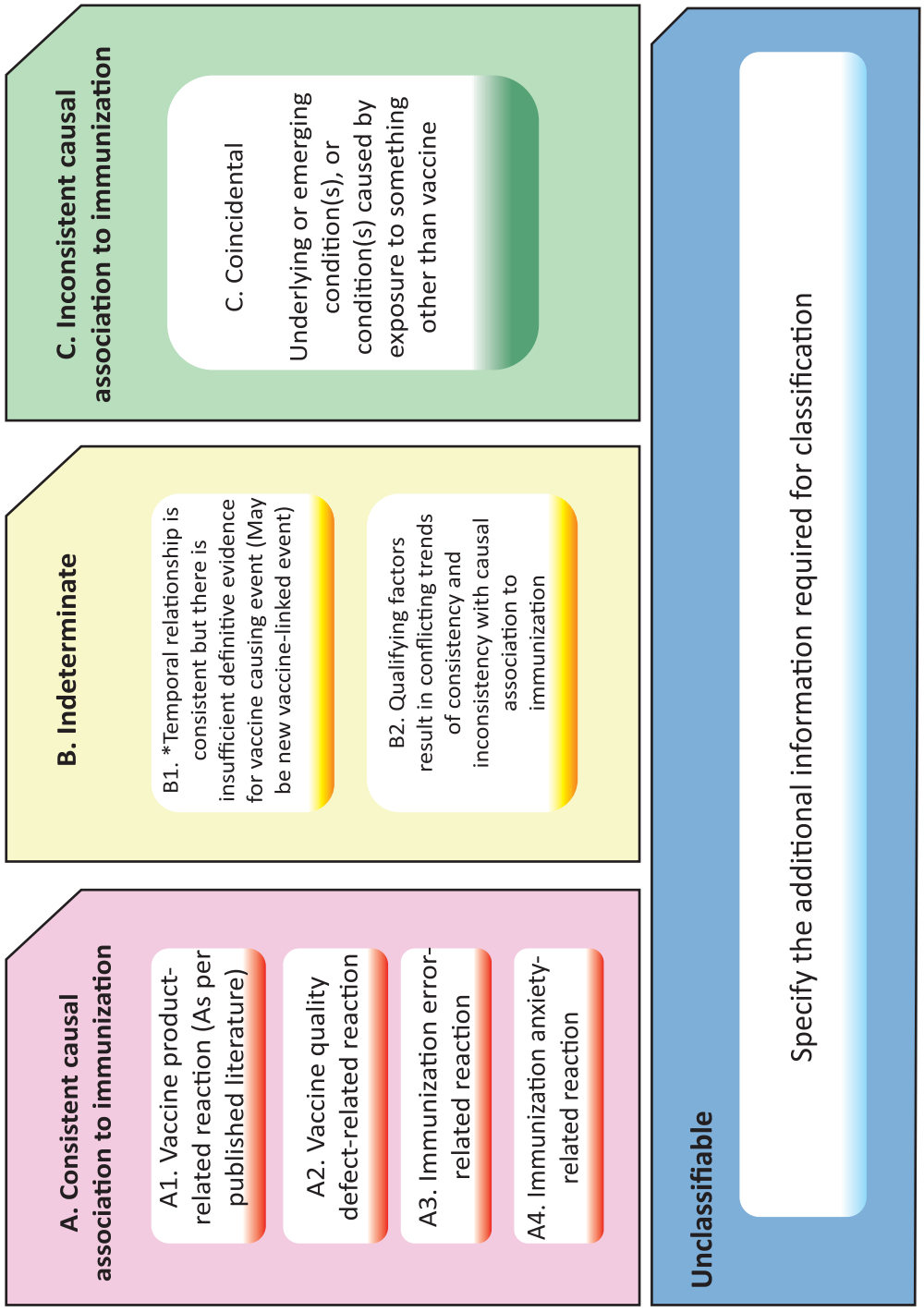
C. This could be due to underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine. Example – a child dies after DPT vaccine and autopsy shows congenital heart disease, or fever occurs after vaccination (temporal association) and malarial parasite is isolated from blood.

D. Adequate information not available (unclassifiable)

D. A case without adequate information for causality conclusion is "unclassifiable" and requires additional information for further review of the causality. All efforts should be made by the state to procure additional information. The available information on unclassifiable cases should be placed in a repository or an electronic database. This database should be periodically reviewed to see if additional information is available for classification, and to perform analyses for identifying signals.

Figure 8.4 gives the classification of casualty assessment.

Fig. 8.4. Causality assessment: classification



*B1 : Potential signal and maybe considered for investigation

States are encouraged to adopt the new revised causality assessment process during the expert committee reviews. The final classification (Step 4) is critical, as it provides directions for the follow-up actions. It is important to note that the final classification of a given AEFI may change with updated knowledge and information.

When AEFI occur as clusters, it is important to consider each case separately, do an independent causality assessment for each case in the cluster and classify the same. After classification, the cases should be line listed to see if a pattern emerges. Pattern identification is important for action to be taken as well as in identifying signals.

In case of –
Multiple vaccines to the same patient
Each vaccine should be assessed separately
AEFI cluster
Each patient in the cluster should be separately evaluated

8.6 Actions to be taken after causality assessment

Regardless of the outcome of causality assessment, the lessons learned should provide insights for the technical, immunization programme and administrative managers regarding the immunization programme. Findings should be promptly and clearly communicated and the messages should be clear on any next steps to be taken, including communicating reassurance or the need to take action around the programme including training, research, modifying systems, refining tools and so on, to avoid and/or minimize recurrences.

A. Consistent causal association to immunization

A1. Vaccine product-related reaction

State AEFI committee should review whether these events occur at a rate higher than expected. In such cases it should inform DC (Immunization).

A2. Vaccine quality defect-related reaction

If this 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 DC (Immunization), the national regulatory authority (DCGI) and the marketing authorization holder (the pharmaceutical company) about the AEFI. The event should be communicated to the manufacturer through these bodies.

A3. Immunization error-related reaction

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

A4. Immunization anxiety-related reaction

Vaccination should take place in an ambient and safe environment.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

The details of such AEFI cases are to be maintained in a national database at the AEFI Secretariat. The state AEFI committee should also store the details for future reference. This can later 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.

B2. Conflicting trends of consistency and inconsistency with causality

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)

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

D. Follow-up actions

It is never appropriate to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established, a further investigation or epidemiological study may be warranted depending on the nature of the event, its extent and whether it is ongoing. However, it must be accepted that in some cases the relationship to the vaccine is not clear.

Communication and training are two important follow-up actions, not necessary based on any individual event, but in general for attention by the programme managers at all levels. Communication is separately presented in this manual at Chapter 11.

Actions to be taken on completion of investigation/causality assessment is given in Table 8.2.

Table 8.2. Actions to be taken upon completion of the investigation/causality assessment

Type of AEFI	Follow-up action
Vaccine-related reaction	If a higher reaction rate than expected is observed from a specific vaccine or lot, inform the Immunization Division who can update drug regulators to consider: – withdrawing that lot – changing manufacturing specifications or quality control – obtaining vaccine from a different manufacturer.
Immunization-related errors	Correcting the cause of the error. This may mean one or more of the following: – change in logistics for supplying vaccine – change in procedures at the health facility – training of health workers – intensified supervision. Whatever action is taken, it is important to review it at a later date to check that the immunization-related errors have been corrected.
Coincidental	The main objective is to present the evidence showing that there is no indication that the AEFI is a vaccine-related reaction or an immunization-related error and that the most likely explanation is a coincidental event. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes it may be useful to enlist further expert investigation to convince/ensure that the event truly was coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.

Summary

- Causality assessment is the systematic review of individual or population data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine/s received.
- The quality of the causality assessment depends on factors such as the effectiveness of the reporting system and the quality of the causality review process. The causality assessment committees at the state and national levels should be adequately trained.
- Whether an AEFI is attributable or not to the vaccine or the vaccination programme, causality assessment determines what steps need to be taken to address the event.
- The response and follow-up for the AEFI will depend on the findings of the investigation.
- It is worth disseminating the results of the investigation so that others can learn from the experience. The investigation can also make a useful teaching resource in training investigators in the future.
- Immunization errors will need to be corrected. There should be a checking mechanism to ensure that they do not reappear.
- For coincidental events, the main task is communication to maintain confidence in the immunization programme.
- Training is an important component in the vaccine safety surveillance system and its follow-up activity. Programme managers should use this as an opportunity to strengthen the immunization programme in the country.

9

AEFI committees and monitoring of surveillance

AEFI committees are established at the district, state and national level. The responsibilities of the AEFI committees are to strengthen AEFI reporting at all levels, ensure maintenance of national policy and standards, ensure prompt and thorough investigation of serious/severe AEFI, carry out periodic review of AEFI for trends of non- serious AEFIs reported through HMIS/routine immunization reporting, respond to media and community concerns to allay fears regarding vaccine safety, ensure high standards of AEFI surveillance to ensure no serious AEFI are missed and recommend changes to the immunization programme for ensuring vaccine safety. Experts in the committee help in timely classification and assessment of causal association between the vaccine and the event based on the current globally accepted classification and assessment system.

9.1 Composition of AEFI committee

AEFI committees provide technical inputs to review the factors leading to the adverse event and provide inputs to improve the system to provide safe and effective immunization. They are ***not*** *intended to blame any health facility or an individual.*

The following specialists, programme officers and representatives of professional bodies should constitute members of an AEFI committee. The immunization programme manager should be the member-secretary.

- Epidemiologist/public health specialist
- Representative from drug authority
- Paediatrician
- Microbiologist
- General physician
- Neurologist
- Pathologist
- Forensic expert
- Cold chain officer
- Member Integrated Disease Surveillance Project (IDSP)
- Representative (MOs) from local bodies such as municipal corporations
- Members from professional bodies such as IAP and IMA
- Representatives from partner agencies such as WHO, NPSP and UNICEF can be on the panel as ex-officio members and may be invited, when required.

Other members could be inducted as desired by the national, state/region or district committee. If possible, preference should be given for specialists working in medical colleges to chair and be a part of the AEFI committee.

9.2 Terms of reference for AEFI committees at various levels

9.2.1 District AEFI committee

Every district must constitute and establish a functioning AEFI committee with the DIO as the member-secretary. The members in the committee should be locally available persons representing the above mentioned fields whereever possible. The concerned block MO i/c where the AEFI has occurred or the MO who investigated/treated the case could be a special invitee The committee will meet at least once every quarter or earlier when needed.

Terms of reference (TOR) of the district AEFI committee

- Analyze the CRF and plan for investigation of the AEFI as a team
- Provide appropriate inputs to the drug authority to decide on temporarily suspending use of the implicated batch of vaccine/diluent/syringes
- Assist in investigating AEFI cases with technical inputs, when required
- Append signatures to the CIFs based on the findings of the investigation of the AEFI
- Outline the further course of action on the current AEFI
- Analyse programme information, media reports and other sources of information on serious AEFI and ensure AEFI reporting and investigation are of the highest standards
- Analyze and review the quarterly AEFI data for any programmatic errors and suggest remedial measures for the same

- Participate in the state/national AEFI committee meetings for causality assessment, if required
- Monitor and analyze minor AEFI data every quarter
- Support the spokesperson for media communication
- Ensure that the private sector is actively involved in AEFI reporting
- Monitor the timely submission of completed investigation forms (CRF, PCIF, FCIF) along with supporting documents/medical records
- Communicate and share the conclusions and results of investigation with health workers and the community, where warranted
- Any other responsibility in context to vaccine safety that the committee would like to add.

The minutes of the meeting should be shared with the state expanded programme of immunization (EPI) officer after the meeting.

Even if AEFI cases are not being reported from the district, the district AEFI committee should meet to ascertain the reasons for the non-reporting and then take steps to address the issues.

Expenses for these meetings may be made from the available funds from part C (Immunization) of NRHM project implementation plan (PIP).

9.2.2 State AEFI committee

The immunization officer of the state will be the member-secretary in the state AEFI committee. Specialists from medical colleges should be given preference for being inducted as members of the committee. The concerned DIOs and other members of the district AEFI committee where the AEFI has occurred could be special invitees. The committee will meet once every quarter or earlier as per need to fulfill the following TORs:

- Desk review of the CRF, PCIF and FCIF for causality assessment
- 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
- Analysis of similar cases or clustering of cases in the state
- Periodic review of the data base of AEFI cases. Look for districts not reporting AEFI cases for a long time
- Support the spokesperson for media communication

- Ensure district AEFI committees meet every quarter or more frequently as needed and that they fulfil their responsibilities.
- Ensure minutes of the meeting are shared regularly with Secretariat, DC Immunization, Immunization Division within a fortnight of the meeting.

Preparation for state AEFI committee meeting

The state EPI officer should ensure that the following preparations/workup takes place for all the cases to be discussed before arranging a state AEFI committee meeting:

A) Documents and reports

1. Collection of CRF, PCIF and FCIF for all reported cases
2. In cases of reported deaths, final postmortem report (if conducted) and verbal autopsy (in cases of sudden unexplained deaths). All the relevant reports such as viscera report, histopathological report and chemical analysis report should be attached along with final postmortem report
3. Hospital records including doctor's prescriptions/treatment records for reported AEFI and any other illnesses
4. Relevant laboratory reports such as pathology/microbiology test report (blood, CSF, urine)
5. Standard quality reports for vaccine/syringes/drug (if sent for testing)
6. For cluster cases, a common case summary should be prepared for expert review
7. Any other documents such as field investigation report, media reports about cases, etc.

B) Resource persons

All the state committee members should have prior information about the meeting and members should be encouraged to attend meetings on a regular basis

DIOs and other members of the district AEFI committee where AEFI has occurred could be special invitees

National Immunisation Division may be provided prior information about the meeting so that experts from national level may participate when needed.

C) Logistics

Blank forms such as causality assessment forms

Relevant literate for ready reference, e.g. Brighton collaboration definitions, case reports, vaccine safety reports, WHO fact sheets and relevant published articles

Audiovisual aids, writing pads, pens, pencil, marker

D) Programme performance report

Analysis should be done with the help of indicators for monitoring of AEFI surveillance programme and analysis of AEFI data (mentioned in Section 9.3).

9.2.3 National AEFI Committee

The National AEFI Committee should have sector-wide membership including paediatricians, community health experts, immunologists, pharmacologists, forensic medicine experts as well as representatives from the professional bodies such as IAP, IMA, etc.

The National AEFI Committee will review selected serious and severe cases and will provide a feedback within three months of receipt of state AEFI committee causality assessment reports.

The TORs of the Committee are as follows:

1. Provide technical guidance on policy and implementation to the national AEFI surveillance programme
2. Update and review AEFI programme guidelines and SOPs and establish systems for ensuring quality data
3. Provide support for strengthening AEFI surveillance in states through handholding and facilitating training and workshops as and when required
4. Review the trends of AEFI reports on a regular basis and suggest policy interventions
5. Review reports of causality assessment from the states and assist states in field investigation if required
6. Conduct periodic evaluation of AEFI surveillance in the country
7. Suggest processes for greater integration of the private sector in the AEFI programme, including reporting, investigation and response
8. Strengthen integration with the National Pharmacovigilance Programme with partners including CDSCO and Indian Pharmacopoeia Commission (IPC).
9. Advice the National AEFI Programme on improved vaccine quality and testing facilities and collaboration with national/international institutions
10. Suggest issues within AEFI surveillance which require research (operational/implementation) and pilot studies to improve AEFI surveillance
11. Provide feedback to reporting sites and strengthen AEFI case management and closure.

There are four subcommittees of the National AEFI Committee. Each subcommittee has a chair and is responsible for specific activities.

1. Causality assessment subcommittee – conducts quarterly causality assessment at the national level to review trends and identifies signals in the context of introduction of new vaccines

2. Investigation subcommittee – undertakes an AEFI field investigation as and when requested by the Immunization Division, MOHFW and provides help in follow-up actions to improve AEFI investigations

3. Laboratory subcommittee – supports identification and establishment of a network of national/accredited laboratories across the country for testing vaccine and AEFI case samples, coordinates with the CDSCO and suggests ways and methods of ensuring quality laboratory tests and standards as applied at a global level for AEFI case investigation

4. Media subcommittee – Addresses the media at national/state level to handle communications pertaining to AEFI, identifies and establishes a network of spokespersons at the state and district level, develops an appropriate communications curriculum and communication aids/kits.

9.3 Monitoring the performance of the AEFI surveillance system

The AEFI surveillance system needs to be regularly reviewed at all levels to ensure that the system is sensitive enough to identify and respond to AEFI rapidly. Key indicators which can be used to monitor the performance of the surveillance system are discussed below.

9.3.1 Monitoring routine AEFI reports

1. Percentage of routine reports (zero reports) received on time

No of routine reports (zero reports) received weekly / No of expected routine reports in the same time period x 100 **≥ 80%**

2. Percentage of AEFI cases line listed

No of AEFI cases (serious and severe) line listed in the week/ No of AEFI cases (serious and severe) identified in the week x 100 **≥ 90%**

3. Percentage of serious AEFI cases

No of serious AEFI cases / No of serious and severe AEFI cases x 100 **No target**

9.3.2 Monitoring serious AEFI reports

4. Percentage of serious AEFI cases reported on time

No of serious AEFI cases reported to the district health system using standard forms within 24 hours of case notification / No of serious AEFI cases x 100 **≥ 80%**

5. Percentage of serious AEFI cases with CRF shared with the state and centre on time

No of serious AEFI cases reported by the district health system using standard form within 48 hours of case notification / No of serious AEFI cases x 100 **≥ 80%**

6. Percentage of serious AEFI cases investigated on time

No of serious AEFI cases investigated and PCIF shared by the district within 10 days of case notification / No of serious AEFI cases x 100 **≥ 80%**

7. Percentage of serious AEFI cases with completed investigation

No of serious AEFI cases with all possible information collected and documents shared by the district within 70 days of case notification / No of serious AEFI cases x 100 **>80%**

8. Percentage of serious AEFI cases classified for causality by the state AEFI committee on time

No of serious AEFI cases reviewed and classified by the AEFI committee within 100 days of case notification / No of serious AEFI cases reported x 100 **≥ 80%**

9.3.3 Analysis of AEFI reports

It is essential that all minor, severe and serious AEFI get reported. In addition to basic time, place and person analysis that should be done by the district and state programme managers from the data received, key analysis outcomes that will help the district document effectiveness of the AEFI surveillance system include:

- number of AEFI reports received monthly (severe, serious and minor AEFI, including clusters)
- classification of reported AEFI by types
- classification of AEFI by antigen
- classification of events by causality assessment
- unusual AEFI
- No of cases labelled as sudden unexplained deaths and availability of their verbal autopsy/forensic autopsy forms
- cases identified as immunization errors and corrective measures taken.

10

Operational aspects of AEFI surveillance

An effective immunization safety surveillance system must be able to detect and conclusively classify AEFI in order to prevent their occurrence and/or reduce their impact. The surveillance of AEFI in India was first initiated in 1986.

10.1 Goals and objectives of AEFI surveillance

The overall goal of AEFI surveillance is to reduce morbidity and mortality due to AEFI and minimize the negative impact of AEFI on public health.

The specific objectives of AEFI surveillance are to:

- Promptly detect, report and respond to AEFI
- ☞ Identify unusually high rates of AEFI related to a specific vaccine lot/brand
- Promptly address programmatic errors through implementation of corrective measures
- Estimate serious AEFI rates in the population and compare these with local and global data
- Identify signals of unexpected adverse events and generate new hypotheses about these events that must be confirmed by planned studies and laboratory investigations.

10.2 Key elements of the AEFI surveillance system

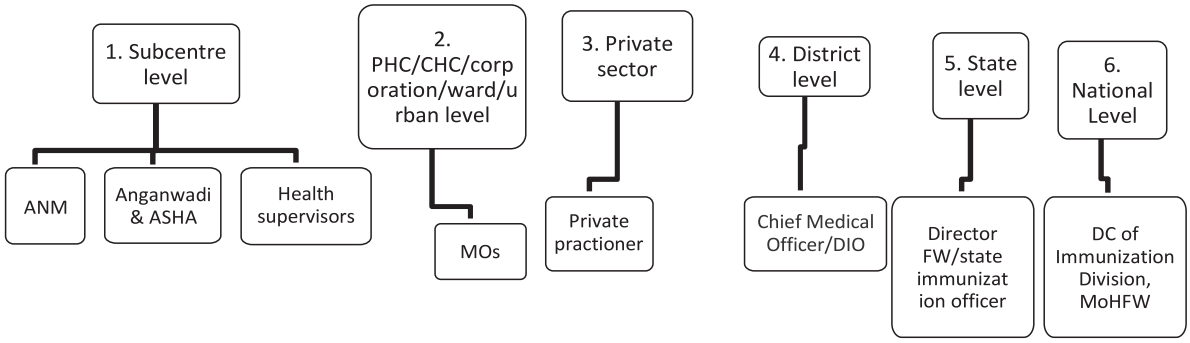
The AEFI surveillance system comprises of the following elements:

- Well-defined standard operational procedures to ensure clarity and uniformity, and avoid duplication of efforts
- Adequate education and training of key personnel
- Rapid notification and evaluation of AEFI information followed by effective response
- Maintenance of an AEFI database for comprehensive analysis at appropriate levels.

10.3 Roles and responsibilities of key players

The AEFI surveillance system involves a network of key players. The surveillance system and its key players are given in Figure 10.1 and discussed below.

Fig. 10.1. AEFI surveillance system and key players



10.3.1 Community level

Anganwadi and ASHA/volunteers/frontline workers

- Follow up with beneficiaries to identify AEFI after vaccination session using the beneficiaries list provided by the ANM
- Pass information of any adverse event immediately by telephone to concerned ANM, MO and other concerned persons
- Assist in referral of any suspected cases
- Assist the team investigating the event
- Support in building community confidence.

10.3.2 Sub-centre level

ANM

- Follow best immunization practices. Prior to starting vaccination at the routine immunization (RI) site, the ANM must note down the following particulars. This will help mitigate AEFI at session site level:
  - manufacturer's name
  - expiry date
  - batch number
  - VVM status (for new and partially used vaccines)
  - date on the label of partially used vaccine (in case of open vial policy).

- Ensure that vaccine septum has not been submerged in water or contaminated in any way.
- Provide a list of children vaccinated in the session to the AWW/ASHA and request them to be alert and to follow up and report AEFI (if any) to her and the concerned MO.
- Ensure reasons for drop-outs are entered in the immunization card counterfoils.
- Treat minor AEFI (mild symptoms like fever, pain, etc.) symptomatically.
- For all other cases (serious/severe), provide immediate first aid and refer the AEFI to the MO (PHC) or to the appropriate health facility for prompt treatment and reporting. Inform the MO (PHC) at the health centre immediately by the fastest means possible.
- Share details of all AEFI (serious/severe and minor) 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 case register maintained at the block PHC (*see* Annexure 9 for suggested format for AEFI case register).
- Assist in investigation of AEFI and take corrective action in response to the guidance from the MO (PHC).

Health supervisors (HS)

- Supervise and provide hands-on training to the ANMs/vaccinators in the field. This includes provision of information on referral transport and concerned officials in case of crisis.
- Monitor the community for adverse events during their supervisory visits to immunization sites or sub centres. 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 AEFI. The serious/severe AEFI should be notified immediately by the fastest means possible.
- Analyze the reported AEFI in the sub-centre monthly 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.

10.3.3 Block PHC/CHC/corporation/ward/urban health post level

MO i/c

– **Detection of AEFI**

  - Train staff in detecting, managing and reporting of AEFI and differentiating between minor and serious/severe events. Encourage the staff to report AEFI.
  - During case visits, enquire about any recent outbreak of disease/illness or any death in the community which may or may not have been related to vaccination.

The line list of serious, severe and minor AEFI should be maintained at the block PHC/CHC in the AEFI register

Details of serious and severe AEFI should be submitted to DIO in weekly reporting in the H002 form

Please ensure filing of weekly nil/zero report in case no serious/severe AEFI is notified

– **Management of AEFI**

  - Clinical case management of AEFI and referral to the next level if required
  - Ensure availability of emergency drugs and medical equipment to deal with an adverse event. Regularly check the emergency kits for functional status of equipment and expiry of drugs.

Involvement in AEFI surveillance can be increased by involvement of professional organizations such as IAP and IMA. IAP has also set up online software for reporting of infectious diseases (IDSurv). This has provision for reporting of AEFI.

– **Reporting of AEFI**

  - Ensure timely notification of AEFI from sub-centre to PHC. Ascertain that ANMs provide details of all serious, severe and minor AEFI in their areas on a weekly basis. A weekly nil report from the ANM gets submitted only after an effort has been made to look for these events in the children recently vaccinated.
  - Detailed information of all serious, severe and
  - AEFI notified by health workers should be recorded in the AEFI register.
  - Ensure weekly submission of information of the No of serious/severe AEFI cases to the district in the H002 form.
  - Conduct timely visits when cases are notified. Fill up the section A of the CRF completely and submit the same to the DIO.
  - Maintain quality—good clinical history, pre and post vaccination health status, community investigation, etc. during interview and documentation.
  - Ensure follow-up and collection of all relevant records including hospital records, laboratory records and other reports for all AEFI hospitalization cases which have

been reported and investigated, and submit the same to the DIO.

- Track and collect postmortem reports, histopathological reports, toxicology reports and final cause of death reports in AEFI death cases in which postmortem has been conducted and submit the same to the DIO.
- Ensure adequate supervision and monitoring in the field.
- Communicate and share the results of investigation with health workers and the community wherever warranted.

10.3.4 Private sector

The private sector in India plays an important role in providing immunization services.

- In rural areas, they at times improve access to basic vaccines, fill gaps in service delivery and are more flexible with timings and approachability.
- In urban areas, the private sector functions as a provider of new and underutilized vaccines and quickly adopts new vaccines and technologies before adoption by the public sector.

Thus, AEFI detection, management and reporting by the private sector are important to ensure timely and complete information about conventional vaccines as well as new vaccines and technologies. Private practitioners are encouraged to report AEFI to the nearest govt health-care facility or the DIO. The CRF could be used for notification of cases (Annexure 1).

AEFI surveillance can be improved by involvement of professional organizations such as IAP and IMA. IAP has online software for reporting of infectious diseases (IDSurv). This has provision for reporting of AEFI.

10.3.5 District level

DIO/CMO

Pre-event

- Establish that a functional district/corporation (or local body) AEFI committee with defined terms of reference and responsibilities is in place. Ensure that in addition to other experts, the drug inspector is a member of the district AEFI committee.
- Ensure that adequate documentation of the AEFI system is maintained and available at the district level. This should include a contact list of AEFI committee members at various levels, terms of reference of the AEFI committee, line listing of serious and severe AEFI cases investigated, completed reporting formats (CRF and CIF) and their supporting documents, spot maps and other AEFI related communications such as letters, government orders(GOs), bulletins, state AEFI committee meeting minutes, feedback, vaccine sample results, etc.

- Ensure that a line list of all serious/severe and minor AEFI cases which were notified and reported but not investigated is maintained, as well as a folder with the CRFs citing reasons why the cases were not investigated. Discuss each case not investigated in the next district AEFI committee meeting to ensure that no AEFI case deserving to be reported and investigated is ignored.
- If the committee does find such a case, a decision should be taken to initiate the investigation procedure. The state and national authorities should be updated accordingly.
- Coordinate with the ADR monitoring centres of the PvPI to ensure that the ADRs 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 the government/private medical colleges in the district to identify specialists to assist the district AEFI committee in investigations, e.g. neurologists, forensic medicine specialists, microbiologists and histopathologists.
- Build relations with and advocate reporting of AEFI with members of district chapters of IAP and IMA.
- Ensure that the personal contact details of the DIO are shared with appropriate staff in the govt, autonomous bodies and private institutions undertaking vaccinations to ensure prompt reporting of AEFI.
- Ensure that key updates of the district AEFI committee meetings are discussed and reviewed during the monthly district task force for immunization meetings.
- Ensure availability of adequate reporting forms (weekly reporting forms and CRF) and adequate logistics such as AD syringes to prevent AEFI due to programme errors. The weekly report should be included in the same performa that reports AFP and measles cases (H-002). Accordingly, the district report should be shared with the state in the weekly D-001 form.
- Ensure AEFI guidelines are disseminated and staff trained and sensitized to detect and respond to adverse events in time.
- Identify nodal persons in institutions for reporting adverse events. These can be the same persons who are presently supporting AFP and vaccine preventable disease (VPD) surveillance.
- Review data; analyze AEFI reported through weekly reporting, HMIS and other reporting channels in the district. Discuss AEFI surveillance as part of the monthly MO meeting and share feedback with state and block PHCs/CHCs in the district.

Event

Complete the CRF and share the form with state and national level functionaries within 24 hours of submission by the MO

Investigate all serious/severe AEFI in coordination with the district AEFI committee at the earliest

Ensure timely management of all cases in the district including coordination with local hospitals/laboratories from the govt sector, medical colleges and other private hospitals to deal with any referral/testing or other procedures following AEFI

Send CRFs and CIFs from district to state EPI officer and Immunization Division as per timelines

The documents should be shared with the National Immunization Division at aefiindia@gmail.co

Post-event

Complete the preliminary and final CIF as per the stipulated timeline and coordinate with the district AEFI committee to complete the documentation and submission of the details to the state and national levels

Coordinate with laboratories undertaking sample testing and share the conclusions and results of investigation with appropriate levels

Within a district, a corporation should be considered as a separate entity for AEFI reporting and investigation. It should have its own independent AEFI committee. For AEFI surveillance, the corporation MO (in charge of immunization) should perform activities as conducted by a DIO in a district. After investigation, the corporation MO should send the details of investigation to the state for final causality assessment.

10.3.6 State level

Director FW/state immunization officer and drug authorities

Pre-event

– Coordinate and lead the AEFI activities in the state.

- Establish a functional state AEFI committee (including the state drug authority) with defined TOR and responsibilities.
- Maintain AEFI related documentation at the state level. Available documentation should include the contact list of AEFI committee members, 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 and GOs.
- Ensure that the national AEFI guidelines and reporting formats are disseminated to the programme managers and other staff at the district and sub-district level and that there is a plan to train the staff at periodic intervals.
- 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 AEFI which are not being investigated is up to date and verify that no AEFI worth investigating was ignored.
- The state task force for immunization should discuss and review key updates from the state AEFI committee in its monthly meeting.
- Ensure that the DIOs have an updated list of the ADR monitoring centres in their districts and that they are investigating serious and severe AEFI cases reported by the centres.
- 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.
- Coordinate with the state chapters of the IMA and IAP to ensure reporting by private practitioners from districts. Ensure that the DIOs respond adequately to information of AEFI from the private sector.
- Strengthen AEFI surveillance in the state using the existing surveillance networks.
- Encourage AEFI reporting from both the govt and private sector and encourage submission of **nil** reports from the districts in the D-001 form. The state should accordingly submit their weekly state report to the national level in the S-001 form.
- Ensure effective AEFI monitoring and supportive supervision.
- Review and analyze AEFI reported through HMIS and other reporting channels in the state and share feedback with the GoI and the districts in the state. Identify districts that are not reporting any AEFI or are underreporting AEFI. Review cases reported but not investigated by the districts.
- 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.

- Monitor reported AEFI data for detection of potential signals out of previously unrecognized signals and vaccine-related adverse events and make recommendations for further investigation.
- Review AEFI cases during state and district review meetings and workshops.
- Provide feedback of observations and recommendations of state AEFI committee and specimen testing results to the concerned DIO/district AEFI committees.

Event

Check if similar events have occurred in other districts by review of data. Coordinate with the DIOs and provide technical assistance (e.g. specimen collection and shipment, handling the media) if requested by the district.

Coordinate 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

Engage the state AEFI committee regularly and in a timely manner for final conclusion (causality assessment) of the reported serious AEFI. Ensure the completion of the CIFs and submission of preliminary and final forms as per the stipulated timeline. Coordinate with the district and state AEFI committees to complete the documentation and submission of the details to the national level.

Conduct quality causality assessments of each reported case at the state level within 100 days of notification of an AEFI case.

Ensure submission of all documents including hospital records and postmortem reports for all AEFI cases by the districts.

Ensure that the state communication plan is activated to handle any crises.

10.3.7 National level

DC of Immunization Division, MoHFW

Actions required at the national level include the following:

- Reviewing the overall pattern of reports and investigations, revision of guidelines/SOPs, capacity building at national and state levels, maintenance of the national database of serious and severe AEFI cases and providing feedback to the states
- Conducting periodic evaluation of the AEFI surveillance system of the country
- Arranging and co-coordinating the meeting of the National Expert Committee and sub-committees on AEFI on a regular basis
- Coordinating with the national drug regulatory authority and other stakeholders in vaccine safety
- The AEFI Secretariat supports the Immunization Division in strengthening AEFI surveillance in the country (refer Section 10.5).

10.4 National/state regulatory authorities, central drug laboratories

AEFI is a vital functional component of the National Regulatory Authority (NRA). The NRA is essential not only for assurance of vaccine quality in the country but also for prequalification of vaccines. The core functions of the NRA are:

- Marketing authorization and licensing activities of vaccines
- Post-marketing surveillance including surveillance for adverse events through collection, collation, regulatory action of vaccines based on post marketing surveillance (PMS), periodic safety update report (PSUR) and AEFI reports/data
- Coordination of lot/batch release process
- Laboratory support
- Regulatory inspections of GMP
- Authorization and approval of clinical trials of vaccine
- The NRA and the Universal Immunization Programme (UIP) coordinate the implementation of the AEFI surveillance system at the national level.

Additional roles of NRA, state regulatory authorities (SRAs) and central drug laboratories (CDLs) at Kasauli and Kolkata are as follows:

- Technical point of contact for vaccine testing – receive vaccine samples or initiate collection of samples (SRA/ NRA)

- Advise on vaccine quality and testing at CDLs
- Control and release each batch of vaccine individually, including recalling if necessary by NRA
- Evaluate and monitor vaccine performance including safety (CDL and NRA).

10.5 AEFI Secretariat and zonal AEFI consultants

With the establishment of the state and the district AEFI committees, numerous vaccine campaigns and addition of new vaccines in the immunization program, voluminous data is being received at the national level. It is essential to collate, analyze, interpret and respond to these reports and undertake timely assessment for response. As per the recommendations of National AEFI committee, an AEFI secretariat was established 2012 within the Ministry of Health and Family Welfare to strengthen AEFI surveillance in the country. It is hosted at the Immunization Technical Supportive Unit (ITSU) set up by the MoH& FW, Government of India.

The main functions of the AEFI Secretariat are to:

- **Coordinate with** :
  - Immunization Division, NRA, CDSCO, CBHI, IEC Division, and NCDC, IDSP, WHO / NPSP or other partner agencies to implement NRA recommendations for Post-Marketing surveillance strengthening
  - National AEFI committee (and its subcommittees), National AEFI Technical Collaborating Centre and MoHFW to ensure regular meeting calendar.
  - NRA to implement appropriate regulatory measures and to inform immunization division, MOHFW and the public about AEFI investigation outcomes.
  - Different Central Drug Laboratories to advise on vaccine quality and testing, if needed
  - States and State AEFI committees to ensure continuous monitoring of AEFI to follow up on timeliness & completeness of data reporting in surveillance, response and follow-up of serious AEFIs.
  - Immunization Division, MoHFW and AEFI committee on implementation of activity plan and maintain documentation & publication and provide feedback (program relevant inferences).
  - Liaise with National & International agencies under guidance of Immunization Division, MoHFW

- **Provide technical and program monitoring assistance and capacity building support to:**
    - MoHFW and states to strengthen AEFI monitoring and to conduct investigations and causality assessments.
    - States and State AEFI committees for monitoring of all and especially novel /unknown AEFIs and implementation as well as National policies related to AEFI surveillance and AEFI committee recommendations
    - Design, develop and implement analysis tools, systems and software to provide feedback (program relevant inferences).
    - Develop training material for AEFI monitoring, investigation and causality assessment under guidance of Immunization Division, MoHFW and facilitate National, State and District level workshops and trainings

- **Promote research to strengthen AEFI surveillance**
    - In consultation with NRA and under guidance of Immunization Division, MoHFW, design and implement vaccine safety post-marketing study including methodology and data collection analysis tools.
    - Conduct operational and implementation research for improving AEFI surveillance in the country.

The AEFI Secretariat liases with the other vaccine safety stakeholders including DCGI and PvPI to enhance vaccine safety and contribute to a functional NRA in the country. In addition, since 2014 the MoHFW has facilitated the working of the National AEFI Secretariat by adding key human resources in the form of 4 Zonal AEFI Consultants to liase with the immunization program managers and other vaccine safety stakeholders at the state and district level.

The AEFI Secretariat receives constant guidance and support from the National AEFI Committee and has established collaboration with Lady Hardinge Medical College, New Delhi designated as the National AEFI Technical Collaborating Centre (NATC) to provide technical oversight and support to the AEFI Secretariat. This is ensured through a regular meeting calendar to review program progress, provision of technical support to states on immediate (crisis) and regular basis for strengthening AEFI surveillance capacity, review scientific trends in reported AEFI, develop surveillance quality management systems and identify research areas as needed. It is aimed to replicate and institutionalize such a model at zonal level also to ensure sustainable improvement in quality of AEFI surveillance

10.6 Liaison with the district administration and police

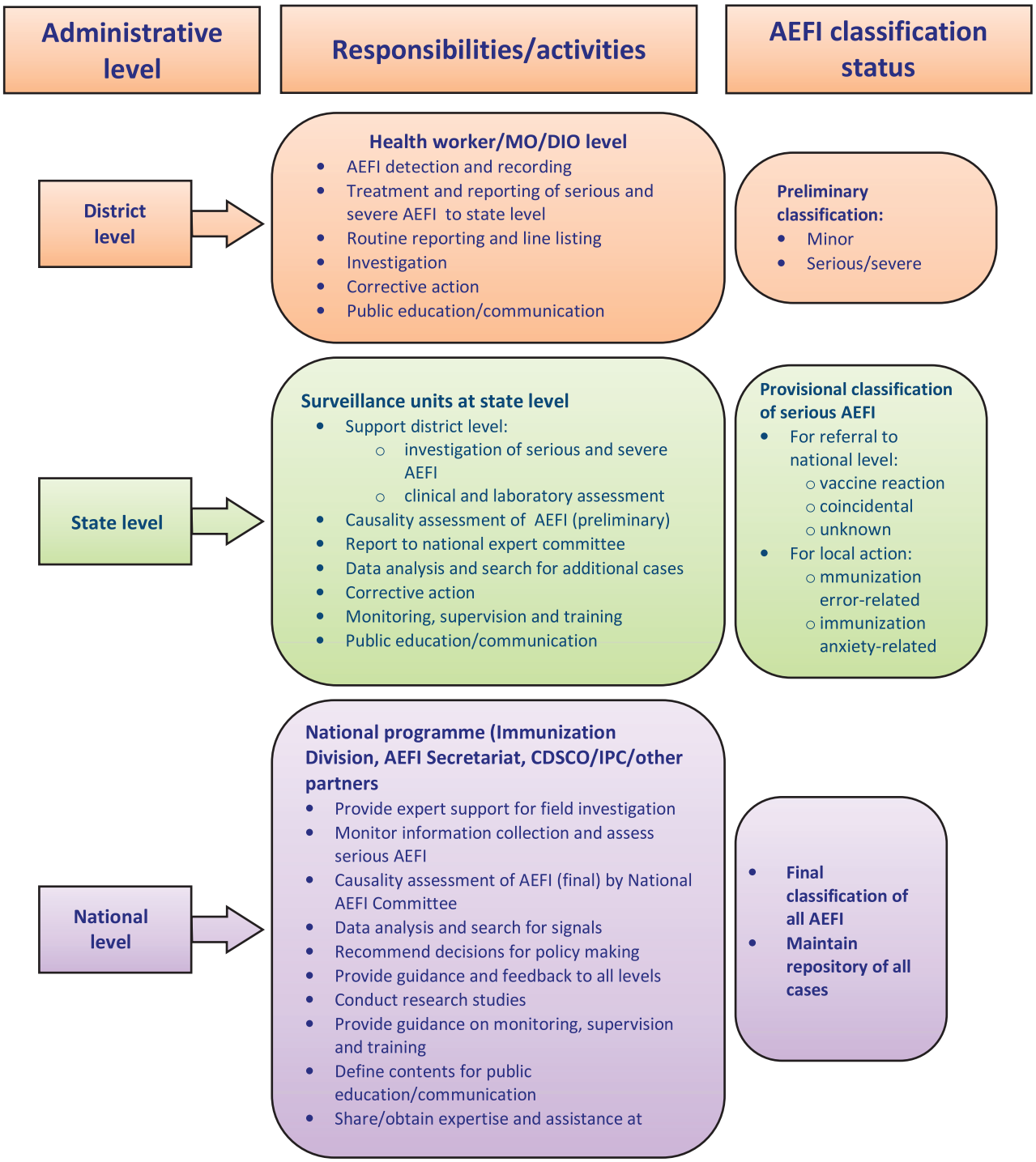
Police officers and the district administration work in partnership with the public. They are citizen focused and respond to the needs of individuals and communities.

Serious AEFI 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. They 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—to arrive at a conclusion on the cause of the adverse event that resulted in death. The AEFI committees are therefore encouraged to 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. 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.

Programme implementation responsibilities and activities at various levels are given in Figure 10.2.

Fig. 10.2. Programme implementation responsibilities and surveillance activities



11

Vaccine risk communication and handling of media

A strategic communication plan should address both short-term crisis situations (such as the occurrence of an AEFI) and long-term support that the immunization programme requires both at the national and local level.

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

The stimulatory effect of communication on health programmes can be effectively routed for developing strategies around RI. In order to have a sustainable impact on the behaviour of individuals and groups on a large scale, communication efforts need to be strategic, participatory, based on evidence from research, result-oriented and well funded.

11.1 Regular communication during RI

Regular communication with the community and local media on RI activities to encourage use of vaccines will help to increase vaccine coverage levels. Health functionaries at all levels should be proactive in this.

ANMs, AWWs and ASHAs can communicate most effectively at the community level using interpersonal communication. MOs, block extension educators and other health functionaries can help community leaders and panchayat functionaries understand the need for vaccination and realize that the benefits of vaccination are overwhelmingly larger than the miniscule number of AEFI which may occur. At the district level, the DIOs and members of the district AEFI committees can proactively reach out to community leaders, religious leaders, district administrative functionaries and reporters/editors on the work being done by the govt in the field of immunization in the district.

The idea is to provide regular, credible and positive information on immunization and other related health programmes to the community and the media. Regularly communicating with the community and the media will improve relations between health providers and communities, encourage community involvement, hone the interpersonal communication skills of health-care

providers, provide counselling services for caretakers and enhance supportive supervision skills at all levels.

It is important to identify and advocate with "custodians" (keepers of good and positive relationships with the community) such as government officials, consultants and NGOs who are in regular touch with the community to make rigorous efforts in encouraging vaccinations. Such efforts will prevent the community from losing confidence in vaccinations and reduce the occasional negative public opinion related to immunization.

It takes a lot of effort, patience and resources to maintain the trust and goodwill of the community and media in the vaccination programme. It has to be a sustained effort and should not wane after the initial enthusiasm. If the community and the media trust 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.

11.1.1 Building confidence in vaccinations to decrease fear of AEFI

Unsupported fear, anguish, concerns and anxiety about vaccine safety are a growing threat to immunization coverage. Internet and social media allow mass diffusion of misinformation and opinions irrespective of their accuracy or authenticity. Hence, if effective communication is exercised at all levels, it can avert the possibilities of a crisis. If at all a crisis occurs, it can be managed by following the steps given in Figure 11.1 below.

Fig 11.1. Managing misinformation

Note: For details about each step refer to "Communication guidelines for building vaccine confidence around AEFI".

11.1.2 Interaction with health workers

Capacity building of health functionaries

Health functionaries at every level—doctors, frontline workers (ANMs, ASHAs, AWWs) and vaccinators should be oriented and empowered to handle queries from the community, especially from parents. Moreover, they should be equipped with technical information on possible adverse events and supported by key spokespersons at local and national levels.

Stop the blame game, support the health workers

Whenever a serious AEFI occurs, the security of the local health worker and vaccinator has to be safeguarded, as they might become targets of resentment or be confronted by affected community members. One has to be prepared to tacle this situation. Efforts should be made to sensitize the police department that the health worker needs to be protected against any public outrage. Instead of blaming the health worker(s), the focus should be on correction and enhancing the quality of the immunization programme. Health workers should also be kept updated on the investigation process, progress and findings.

11.1.3 Interacting with families and communities

Respond in a prompt manner

An immediate response to the bereaved family the moment an AEFI occurs is a good response.

Disseminate key messages and combat rumours

Timely dissemination of a consistent set of easy to understand key messages to concerned families and communities will help to appease their anxieties and reaffirm their faith in the health system.

For serious or severe AEFI, follow the key action points listed in the "Communication guidelines around AEFI".A brief summary is at Table 11.1.

Table 11.1. Key action points for serious/severe AEFI

Serious /severe AEFI such as death/hospitalization/cluster		
Level of intervention		**Communication action points**
Community level	Health worker	• Meet the family – parents/ caregivers and empathise with them • Listen patiently to what the parents/public is saying • Ask some village elders and/or 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 their well-being • Respect their space • Send the information to the MO/DIO immediately
Block level	MO	• Take the most trusted health worker along when you go to meet the family • Take control of the situation and reassure the community without appearing judgemental • Keep people and media informed with facts and accurate information • If facts are not yet ready, inform them that the matter is being looked into and the facts will be out in ___(specify time limit) • Understand risk perception of the family/community • Disseminate timely and accurate messages • Get to the source of information and check factual accuracy of the information

District level	DIO	• Investigate the report completely and in time • Conduct a meeting of opinion leaders and journalists who are supportive to discuss the situation and find possible solutions and a way forward • Understand the community's perception towards immunization and vaccination history of other children in the family • Identify support groups from within the community who could be positive role models in your approach and help convince the community that vaccination at large is beneficial for children • Respond to negative media questions with positive answers
State level	State EPI officer	• Do not bombard the family with visits • Respect their space • Share feedback with community representatives • Review media coverage reports – look into the style and accuracy of reporting • Prepare a database of print and electronic media journalists who cover health at the state level, with their contact details • Identify and prepare a list of supportive and unsupportive journalists • Identify spokespersons and orient them on how to respond to various issues • Disseminate a consistent set of easy to understand key messages at appropriate times to concerned families and communities to help allay their anxiety and reaffirm their faith in the health system • Organize deliberations for journalists. This will help identify, in advance, the specific questions or concerns that journalists have • Organize orientation workshops and field visits for journalists. This will help them gain a better understanding of the advantages of immunization as well as complexities of an immunization programme • Involve school teachers to help in conveying the correct information/message(s) to parents/caregivers of children, and educate them
National level	Government official/National AEFI Committee	• Review media coverage reports – look into the style and accuracy of reporting • Prepare a database of print and electronic media journalists covering health at the state level, with their contact details • Identify and prepare a list of supportive and unsupportive journalists • 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 programme and government efforts • Participate in "talk shows" on the issue to negate any negative picture and appease further rumours from rising.

11.2 Interaction with media

The media (newspaper, radio, television and social media) plays an important role in the formation of public perception. The role of the media is critical as the messages disseminated by the media could brand or blemish the programme. Media is likely to publicize events in case AEFI results in death or disability, or the national press has unearthed "threatening facts", or where they have obtained information before the health professionals have done so. When there is no crisis, interact with the media regularly and keep informing them of the good work being done in the routine immunization programme.

11.2.1 Media management in routine situations

As part of the ongoing communication support to the RI programme, an effective communication plan should be in place before an immunization campaign starts. Effective communication with the media necessitates a plan, a budget, trained personnel, efficient coordination with the field staff and practiced responses to potential issues around AEFI.

A good media plan consists of the following (detailed plan given in Communication Guidelines for Building Vaccine Confidence around AEFI):

- Database of journalists: make a list of reporters and keep their contact numbers and e-mail IDs handy.
- Monitor the media for reports from time to time.
- Information package: give out regular RI press releases for the media using the RI press release template (see samples below) and regularly keep in touch with reporters. Provide them with information and news about the latest immunization activities and push stories – using state-specific RI factsheets – which create a positive environment about immunization and encourage people to have their children vaccinated.
- Develop spokespersons to respond to media queries from time to time.
- Organize orientation workshops and field visits for media personnel.
- Develop a crisis communication operational plan.

11.2.2 The AEFI response protocol – managing media when an AEFI has occurred

The AEFI response protocol is essentially an operational plan, developed to prepare for a crisis situation. It is a recommended response system meant to be of help the next time there is media interest in the AEFI. First and foremost, it identifies the spokespersons who will respond in crisis situations at the national, state and district levels. It is meant to identify a crisis quickly and help the programme reach out and respond appropriately – killing speculations or at least making sure that the scientific and programme point of view is conveyed, creating confidence in the programme.

The protocol also creates a standard procedure for communications to make the process faster. It lists SOPs or activities required to resolve the AEFI crisis and enables the govt spokespersons to respond appropriately using editorial tools such as AEFI response templates, state RI factsheets and ready reckoners to help them deliver uniform messages 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.

* Spokespersons should be identified, trained and authorized to support media response activities. The districts and states should also identify a second spokesperson to cater for times of need or in an emergency – one who is authorized, can give out factual information and has some experience in handling the media.

*All state immunization spokespersons are to be notified immediately about any media report and query from all administrative levels using the fastest means of communication, e.g. by e-mail or phone.

Some frequently asked questions by media:

- Why did this crisis happen? Was the government sleeping?
- Could the situation have been averted had the resonse been timely and adequate?
- What do you have to say on the occurrence of this incident?
- Who is at fault for this loss and crisis?
- How does the govt plan to handle the situation?
- What is the relief being provided to the affected families and communities?
- What are the actions taken so far?

* If there is a crisis and the reports reach the national media, a press release should be issued as early as possible (preferably within the first 6 hours). The central government RI spokesperson must respond at the earliest. Action to be taken at the district and state levels is given in Table 11.2.

Table 11.2. Actions to be taken on media queries

District Level	
Authority	**Action points**
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 to access first-hand information. This will help get credible and timely information to the media, killing speculations and building trust as a credible source. When a media query arises, talk to the media and share factual information which can be verified. The information should be non-speculative and should not trivialize the event. The message should include that the govt is aware of it, is investigating the said AEFI and is also tracking the developments in the field. In case the media persists, for example if there are more than a couple of queries, or it is felt that some journalists may misinterpret the message, then it is better to give out a written response/press release (using district AEFI response template at sample below)

	Share the written response with all the state officials and immunization offices at state and national level simultaneously (since they may get media queries as well). Responses to media have to be time-bound. Factual and timely information will kill speculations. **Recommended timelines/responses 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 the state spokesperson • Get back to the media with more information/developments as promised. Also, direct the media to talk to trusted nongovernment specialists doctors/experts to support queries on vaccine safety. Keep the expert informed and motivated to speak. Groups like IAP, Rotary International 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 did not reach out to the district/state immunization office but has reported on AEFI cases, 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 such media reports continue, ensure that a statement is prepared and mailed to the reporter or the newspaper office or put it up on the website. Depending on how the active the media is in the district, the editors and journalists of various media should be sensitized about AEFI reporting and surveillance. If the reporter or the newspaper is doing negative stories about the programme without asking for the govt perspective, then a statement with factual information on the AEFI cases and the status of investigation should be prepared and mailed to the editor of the newspaper requesting publishing of the facts or clarifying the issue.
State level	
State immunization officer – state expanded programme of immunization officer (SEPIO)	When media queries arise, follow a similar response protocol as for the districts. 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, killing speculations and building trust as a credible source. When a media query arises, share factual information which can be verified. Talk to the media, killing speculations and give out the message that the state is investigating and tracking the AEFI case. The information should be non-speculative without trivializing the event. The message should include that the govt
	is aware of it, is investigating the said AEFI and is also tracking the developments in the field. Respond with a statement using the state AEFI response template given at sample below. If required, also talk to the media and give verbal answers. Follow the timeline for response according to the urgency of the media queries.

Points to remember

The next time there is 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 needed
- adhere to timelines for responding
- keep higher-ups informed about media queries.

11.3 Communicating with the media

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.

Please refer to the samples below for details of when and how to use these.

11.4 Samples for media communication

1. Press statement

A press statement should include:

- a complete account of the event;
- an outline of actions taken to handle the event or planned to be taken (such as an AEFI investigation);
- a description of the cause of the event;
- an assurance that corrective action has been taken or will be taken;
- information on the 5 Ws and 1H for the 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

A press release must specifically answer the 5 Ws and 1 H for journalists.

- Who is affected? Who 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. Give names and contact details of district/state immunization officers, experts among 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 are 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 a 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; usually no longer than 10 minutes
- Speaker(s) should be experienced on the subject and be 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 him.

4. Press interview

Only a designated spokesperson should give a press 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".

A 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 so as 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, stick to your facts and respond in a cool manner.

SAMPLE PRESS RELEASE

Press Information Bureau
Government of India
Ministry of Health and Family Welfare

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
Health Minister: Government will now ensure that the benefits of vaccination reach all sections of the society, regardless of social and economic status

The Health Minister 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-third 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 the working age group and up to 10 lakh 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 Health 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."

Diarrhoea caused by rotavirus kills nearly 80 thousand children each year and 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 on 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 nine 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.

The Health Minister, 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.

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GENEVA 12 August 2009 - More than 18 million children in India will be immunized with a pentavalent five-in-one vaccine

BACKGROUND

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), 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 27 000 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. Around 9 million sessions are held every year.

NOTE TO THE EDITOR

Vaccines against rotavirus and rubella and the injectable polio vaccine are available 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 endgame strategy for global polio eradication. The vaccine against Japanese Encephalitis is already being given to children in districts from where 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 and Family Welfare: Deputy Commmissioner Immunization- + 91-XXXXXXXXXX

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5. Sample district AEFI response template

District_____(*Madhya Pradesh*). Date_____.As a part of the Universal Immunization Programme, the Government of Madhya Pradesh 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_____and_____. The Government of Madhya Pradesh, through its ongoing efforts, has achieved an immunization coverage rate of _____% in _____ *(year)*.

_____ *(number of)* doses of DPT/IPV/BCG/OPV *(choose the vaccinein question)* have been administered to _____ number of children between (*the dates)* _____and_____.

As a part of routine surveillance, _____ (*number of)* AEFI 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) and investigates the serious cases (such as death and hospitalization) to strengthen the immunization programme.

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/postmortems 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 that 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 5years suffer from_____ *(diseasesspecific to antigen in question, depending on 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.

6. **Sample state AEFI response template**

Bhopal, Madhya Pradesh. Date_____. As a part of the Universal Immunization Programme, the Government of Madhya Pradesh 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 _____and_____. The government of Madhya Pradesh, through its ongoing efforts, has achieved an immunization coverage rate of _____% in _____ *(year).*

_____ *(number of)* doses of DPT/IPV/BCG/OPV *(choose the vaccine in question)* have been administered to _____ number of children between _____and_____(*the dates).*

As a part of the routine surveillance, _____ (*number of)* AEFI have been reported on _____ *(date)* in the district/s_____*(name of district/s),* including _____*(details of case/s, e.g 4 deaths, 3 hospitalizations)* in _____*(months).* The AEFI surveillance system records all minor adverse events (such as rashes, swelling at the injection site, fever) and investigates the serious cases (such as death and hospitalization) to strengthen the immunization programme.

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/postmortems 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 state. 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.

12

National Drug Regulatory Authority of India and its affiliated institutions

12.1 National Drug Regulatory Authority of India (NRA)

CDSCO, under the Directorate General of Health Services (DGHS) in MoHFW is the National Drug Regulatory Authority of India. This organization, headquartered in New Delhi, has the mandate to ensure the safety, efficacy and quality of "drugs" in the country as defined under the Drugs and Cosmetics Act, 1940.

All vaccines are defined as "new drugs" under the Drugs and Cosmetics Rules, 1945 and accordingly regulated under Schedule Y

The state drug control departments are primarily responsible for monitoring the manufacture, sale and distribution of drugs within their respective jurisdiction. CDSCO, headed by the DCGI, is responsible for regulation, manufacture and import of human vaccines in the country.

CDSCO grants permission for the manufacture and import of human vaccines in the country after assessment of the benefits versus risks, innovation versus current standard therapies and unmet need of vaccines, in consultation with the New Drugs Approval Committee (Vaccines) and CDL Kasauli. CDL Kasauli is the appellate laboratory for testing and analysis of human vaccines, as notified under the Drugs and Cosmetics Act and Rules. CDL Kasauli is responsible for laboratory access and lot release functions. In case of an AEFI, CDL functions as an appellate laboratory to test vaccines for physical aspects, sterility, abnormal toxicity and biochemical identities and submits the report to CDSCO and the UIP.

Post licensure, the marketing authorization holders (licensed vaccine manufacturers or importers) are required to submit the PSURs to CDSCO for all vaccines for a period of 4 years. In addition, CDSCO functions in close coordination with the PvPI and Immunization Division of the MoHFW for the continued monitoring of vaccine safety.

12.2. Roles and responsibilities of stakeholders

12.2.1 CDSCO

CDSCO is the NRA for discharging functions under the Drugs and Cosmetics Act, 1940. CDSCO executes its functions through its six zonal offices located at Ghaziabad, Kolkata, Mumbai, Chennai, Hyderabad and Ahmedabad. In addition, there are four sub-zonal offices located at Chandigarh, Bangalore, Jammu and Goa.

The roles and responsibilities of the CDSCO are as per the Drugs and Cosmetics Act and Rules.

- CDSCO is responsible for taking appropriate regulatory decisions and actions on the basis of recommendations of PvPI National Coordination Centre (NCC) at IPC, Ghaziabad and advocacy and dissemination of medicine safety related decisions to stakeholders. The import and export of drugs and cosmetics in the country are also regulated at prominent sea ports and airports in consultation with customs officials by assistant drug controllers and technical officers of CDSCO.
- CDSCO is also responsible for taking regulatory decisions on the basis of analysis of the PMS, PSUR and AEFI data collected by expert committees. As part of the conditions of the marketing authorization (MA), the MA holder is also required to submit PMS/PSUR data after licensure of the product. The PSURs are to be submitted every six months for the first two years of the approval and annually for the subsequent two years. The licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. However, all cases involved in serious unexpected adverse reactions (SUARs) must be reported to the licensing authority (DCGI) within 15 days of initial receipt of information by the marketing authorization holder (MAH) in the format of Appendix XI of Schedule Y, Drugs and Cosmetics Rules, 1945.
- The licensing authority may also advise the MAH to conduct Phase IV trials which go beyond the prior demonstration of product safety, efficacy and dose definitions.
- AEFI cells with designated persons have been established in the CDSCO headquarters and its all zonal offices.
- 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.
- The drug inspectors deputed by the state drug control department and the concerned CDSCO (zonal) office under whose jurisdiction the AEFI occurred, take part in joint investigation along with DIO. The drug inspectors are responsible for collecting the samples of implicated vaccine vials in accordance with the provisions of the Drugs and Cosmetics Act, 1940 in a proper manner and send the same to Central Research Institute (CRI), Kasauli for test and analysis.

12.2.2 Indian Pharmacopoeia Commission

IPC is an autonomous institution under the MoHFW dedicated for setting of standards for drugs, pharmaceuticals and healthcare devices/ technologies, besides providing reference substances and training.

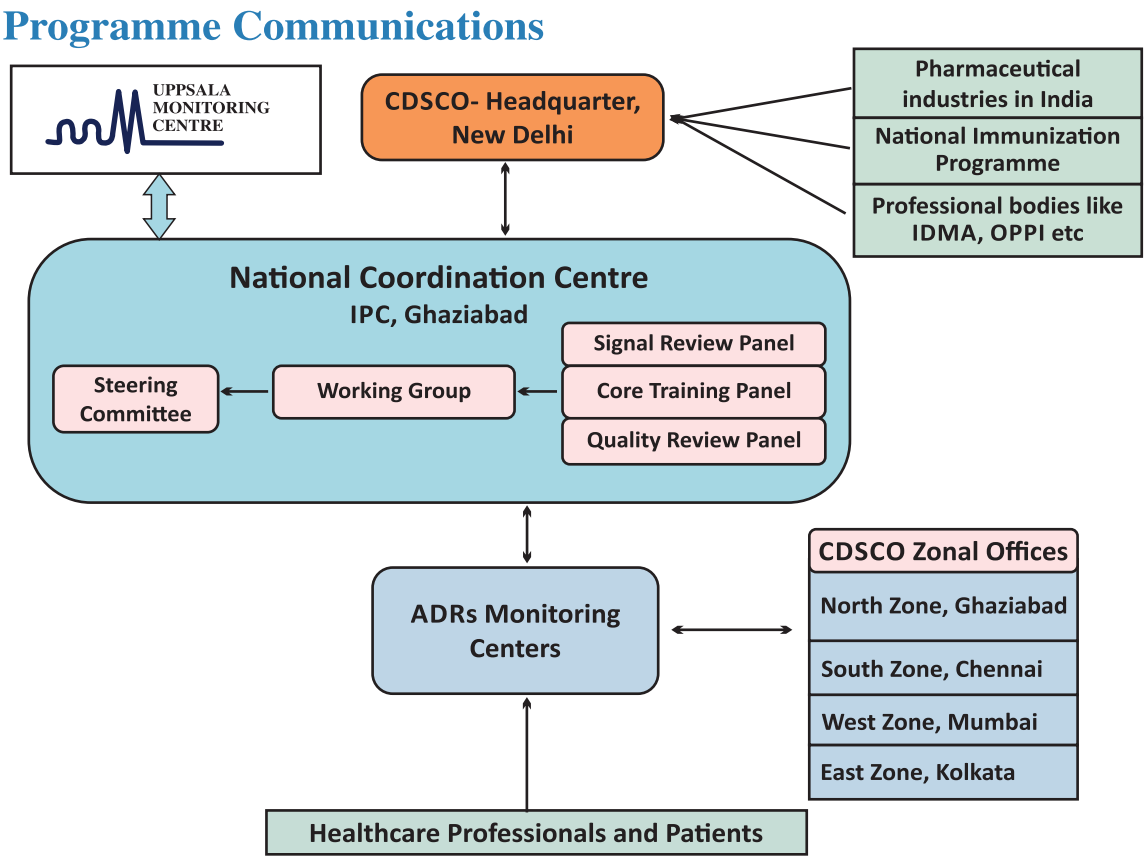
National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI)

WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". This applies throughout the life-cycle of a medicine, equally to the pre-approval stage and to the post-approval stage.

IPC has been functioning as the NCC for the PvPI since 15 April 2011. The main responsibility of NCC is to monitor all the adverse reactions of medicines being observed in the Indian population and to develop and maintain its own pharmacovigilance database for patient safety with respect to the use of medicine including vaccines in India, so that regulatory interventions can be made based on data available in India.

The functioning of the NCC is given in Figure 12.1.

Fig 12.1. Functions of NCC



Role of NCC for pharmacovigilance functions

- Monitor ADRs in the Indian population
- Create awareness amongst health-care professionals about the importance of ADR reporting in India
- Monitor the benefit–risk profile of medicines
- Generate independent, evidence-based recommendations on the safety of medicines
- Support the CDSCO in formulating safety related regulatory decisions for medicines
- Communicate findings to all key stakeholders
- Create a national centre of excellence at par with global drug safety monitoring standards.

Major roles and responsibilities of the IPC include development and implementation of the pharmacovigilance system in India, enrolment of all Medical Council of India (MCI) approved medical colleges in the programme across the country, encourage healthcare professionals in reporting of ADRs and collection of case reports and data in the ADR reporting form.

The details of ADR monitoring centres in India can be obtained from the following web link: http://www.ipc.gov.in/PvPI/AMCsUnderPvPI.pdf

The IPC has established a data sharing arrangement with the AEFI Secretariat for ensuring convergence in vaccine safety reports and their adequate investigation.

12.3 Coordination with Immunization Division under MoHFW

The Immunization Division at MoHFW has established a National AEFI Secretariat and has four zonal AEFI consultants to support AEFI surveillance. The National AEFI Secretariat supports the National AEFI Sub-committee in conducting causality assessment of serious AEFI cases and summarizes the causality assessment reports of reported AEFI. The Immunization Division, MoHFW forwards these reports to CDSCO. Based on the causality assessment reports, detailed inspection related to current GMP, product, etc. and further regulatory actions are initiated by CDSCO in case the quality of the implicated vaccines are indicated to be responsible for the adverse events in the causality assessment report.

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.

Annexure 1

AEFI CASE REPORTING FORM (CRF)

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (to be allotted by DIO)

Section A (To be submitted by MO within 24 hours of case notification to DIO)

State	**District**
Block/ward	**Village/urban area**

Name of reporting MO (person filling this form):	Today's date:
Posted at: Designation:	Time of preparing this form: a.m./p.m.
Contact phone number: email:	Date case visited and examined/interviewed: __ __/__ __/__ __ __ __
Notified by (name): Date notified to MO: __ __/__ __/__ __ __ __	Designation (please circle): health worker/government doctor/private practitioner/community/media/others (specify) _____ _____

Patient's name																				

Date of birth DD/MM/YYYY	**Age** (in months): _____ months	**Sex**	Male / Female

Mother's name																				
Father's name																				

Complete address of the case with landmarks *(street name, house number, village, block, tehsil, pin no., telephone no.)*

P	**i**	**n**	-							**P**	**h**	**o**	**n**	**e**	-												

Date of vaccination: __ __/__ __/__ __ __ __ Time of vaccination: __ __: __ __a.m./p.m.	Address of session site:
Session: Routine (including SIW)* **Campaign** (SIA)-IPPI/MR/JE/others (specify):_____ Other _____	**Place of vaccination:** govt health facility/outreach/private health facility/others ____

Names of vaccines received (write vaccine & diluent details in separate rows)	Dose no. (zero/first/second/etc. as applicable)	Name of manufacturer	Batch/lot No.	Expiry date	Date of opening of vial	Time of opening the vial (for reconstituted vaccine)	No. of OTHER beneficiaries who received vaccine from the SAME vial in this session

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.
Hospitalization: No/yes – (Date)	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.

Name and address of hospital (if hospitalized):

*Special immunization week

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	a.m.		p.m		
Post mortem done? Yes/no/unknown If yes, then write date post mortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, write date planned	H	H	M	M	Y	Y	Y	Y	

Describe AEFI (signs and symptoms):

Suspected adverse event(s) (tick at least one):

☐ Severe local reaction
- ○ *>3 days*
- ○ *beyond nearest joint*

☐ Seizures
- ○ *febrile*
- ○ *afebrile*

☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Intussusception

☐ Fever≥39 °C (102 °F) ☐ Hypotonic hyporesponsive episode (HHE) ☐ Acute flaccid paralysis ☐ Sudden unexplained death syndrome

☐ Death due to any reason other than above – specify……

☐ Hospitalization due to any reason other than above – specify…… ☐ Disability

☐ Cluster – is this case part of a cluster? Yes/no/unknown

If Yes, no of other cases in the cluster _____ (use separate form for each case in a cluster)

Signature and name of reporting medical officer:

Section B: District immunization office to complete and forward to state and national level within 24 hours of receiving the above information

Date case reporting form received at the district: __ __/__ __/__ __ __ __

Proposed date of preliminary investigation: __ __/__ __/__ __ __ __

Remarks:

DIO/district nodal person *(officer forwarding this report)*

Name …… Date……Designation……Mobile No……

Landline (with STD code)…… Fax No. ……

email id…… Complete office address (with Pin code)……

……

……Signature/seal

To be sent to: State Immunization Officer & Deputy Commissioner (UIP),
Immunization Division of Govt of India, MoHFW,
Nirman Bhawan, New Delhi – 110108.
Fax: 011-23062728 **email**: aefiindia@gmail.com

Date report received at state level – __ __/__ __/__ __ __ __

Remarks:

Section C: National level to complete

Date report received at national level – __ __/__ __/__ __ __ __

Remarks:

Annexure 2

PRELIMINARY CASE INVESTIGATION FORM

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (To be allotted by DIO)

Section A Basic details

State	**District**
Block/ward	**Village/urban area**

Place of vaccination: Govt health facility/outreach/private health facility/others (specify) ____

Session: Routine (including SIW) Campaign (SIA)-IPPI/MR/JE/others (specify):_____
Other _____

Name of investigator:	Date case visited and investigated: __ __/__ __/__ __ __ __
Posted at: Designation:	Date of preparing this form:__ __/__ __/__ __ __ __ Time of preparing this form: _____ a.m./p.m. This report is ☐ Preliminary ☐ Final
Contact phone number: email:	

Patient's name																		

Date of Birth DD/MM/YYYY Age (in months): _____ months | Sex | Male | Female |

Mother's name																		
Father's name																		

Complete address of the case with landmarks *(Street name, house number, village, block, Tehsil, PIN No., Telephone No.)*

P	i	n	-							P	h	o	n	e	-												

Date of vaccination: __ __/__ __/__ __ __ __ Time of vaccination: __ __: __ __ a.m./p.m.	Address of session site:
Date first notified to government health system: __ __/__ __/__ __ __ __	Notified by (please circle): Health worker/government doctor/private doctor/community/media/others (specify) _____

Name of vaccines received (write vaccine & diluent details in separate rows)	Dose no. (zero/ first/ second, etc.)	Name of manufacturer	Batch/lot No.	Expiry date	Date of opening of vial	Time of opening the vial (in case of reconstituted vaccines)	No. of OTHER beneficiaries who received vaccine from SAME vial in this session

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.	
Date of key symptom	D	D	M	M	Y	Y	Y	Y	Time of key symptom	H	H	M	M	a.m.	p.m.	
Hospitalization No/Yes – Date	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.	
Name and address of hospital (if hospitalized):																
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	a.m.	p.m.	
Post mortem done? Yes/no/unknown If yes, then write date post mortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, write date planned	H	H	M	M	Y	Y	Y	Y

Section B Relevant patient information prior to immunization

Criteria	Finding	Remarks (If "Yes" provide details)
Past history of similar event	Yes/No/UK	
Adverse event after previous vaccination (s)	Yes/No/UK	
History of vaccine, drug or food allergy	Yes/No/UK	
Pre-existing illness (past 30 days)	Yes/No/UK	
Congenital disorder	Yes/No/UK	
History of hospitalization in past 30 days with reasons (in remarks column)	Yes/No/UK	
Was the patient on any concomitant medication at the time of AEFI? (If yes, name the drug, indication, doses & treatment dates – write in remarks column)	Yes/No/UK	
Family history of any disease (relevant to AEFI) or allergy	Yes/No/UK	

If patient is an adult woman

- Currently pregnant? Yes; Weeks _____/No/UK
- Currently breastfeeding? Yes/No

If patient is an infant, birth details	Any birth complication (specify)
1. Birth weight:	
2. Duration of pregnancy ☐ Full term ☐ Premature ☐ Postdated	
3. Place of birth ☐ Home delivery ☐ Institutional	
4. Delivery procedure ☐ Normal ☐ Caesarian ☐ Assisted	

Section C Details of first examination** of reported AEFI case

Source of information (✓ *all that* apply): ☐ Examination by the investigator ☐ Medical case records ☐ Verbal autopsy ☐ Other_____ If from verbal autopsy, please mention relationship with the deceased_____

In case of sudden unexplained death, please also fill SUD verbal autopsy form as per the guidelines)

Name of the person who first examined/treated the patient_____

Name of other persons from whom care was sought _____

Other sources who provided information (specify)_____

Signs and symptoms (in chronological order from the time of vaccination)

****Instructions** – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, lab and autopsy reports) and then complete additional information NOT AVAILABLE in existing documents, i.e. • ***If patient has taken medical care*** – attach copies of all available documents (including case sheet, discharge summary, laboratory reports and post mortem reports, if available) and write only information unavailable in the attached documents below • ***If patient has not taken medical care*** – obtain history, examine the patient and write down your findings below (add additional sheets as required)

Name of person filling up clinical details given below:	Designation:	Date/time

Consciousness	Alert/Drowsy/Unconscious/Other (specify)_____ Describe:
Vitals	Pulse Temperature Respiratory rate BP Weight
Skin	Rash/Cyanosis/Petechiae/Pallor/Jaundice/Others (specify)_____ Describe:
Eyes	Vision: Normal/impaired Pupil: Normal/Constricted/Dilated/Reacting to light
Hearing, speech	Normal/Impaired: Describe Normal/Abnormal: Describe
Neck	Neck stiffness: Present/Absent
Chest	Auscultation Normal/Crepts/Rhonchi Heart sounds Normal/Murmur (describe)
Respiration	Normal/Cough/Shortness Of Breath/Others (specify)_____ Describe:
GI	Pain abdomen/Vomiting/Diarrhoea/Dysentery/Others (specify)_____ Describe:
Abdomen	Normal/distended/tender Liver: Not palpable/Palpable (If palpable specify size) Spleen: Not palpable/Palpable (If palpable specify size) Describe:
Limbs	Tone • Upper limbs: Normal/Increased /Decreased • Lower limbs: Normal/Increased /Decreased Reflexes

	• Biceps Normal/Increased /Decreased/Absent • Triceps Normal/Increased /Decreased/Absent • Supinator Normal/Increased /Decreased/Absent Plantar Extensor/Flexor

Any other abnormal signs

Treatment provided

Provisional diagnosis

Section D 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												

1. When was the patient immunized? (✓ the ☐ below and respond to ALL questions)

☐ Within the first vaccinations of the session ☐ Within the last vaccinations of the session ☐ Unknown

2. In case of multi-dose vials, was the vaccine given – ☐Within the first few doses of the vial administered ☐ Within the last doses of the vial administered ☐Unknown

3. **Based on your investigation, is it possible that:** *(Please provide explanation for any "yes" answer in the remark column)*

A	There was an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes/No/Unable to assess	Remark
B	The vaccine (ingredients) administered could have been unsterile?	Yes/No/Unable to assess	Remark
C	The vaccine's physical condition (colour, turbidity, foreign substances) was abnormal at the time of administration?	Yes/No/Unable to assess	Remark
D	There was an error in vaccine reconstitution/preparation by the vaccinator (wrong product, wrong diluent, improper mixing, improper syringe filling)?	Yes/No/Unable to assess	Remark
E	There was an error in vaccine handling (break in cold chain during transport, storage and/or immunization session)?	Yes/No/Unable to assess	Remark
F	The vaccine was administered incorrectly (wrong dose, site or route of administration, wrong needle size, not following good injection practice)?	Yes/No/Unable to assess	Remark

4. Number immunized from the concerned vaccine vial/ampoule in this session	
5. Number immunized from the concerned vaccine vial/ampoule since vial was opened (in case of open vial policy)	
6. Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations _____	
7. **Is this case a part of a cluster?**	Yes/No/UK
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/UK
C If no, number of vials used in the cluster	

Section E Immunization practices at the place(s) where concerned vaccine was used

(fill up this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes/No/UK
If "No", specify the type of syringes used: ☐Glass ☐Disposable ☐Recycled disposable ☐Other _____	
Specific key findings/additional observations and comments:	

Reconstitution: (complete only if applicable, ✓ NA if not applicable)

	Status		
• Reconstitution procedure (✓)			
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
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			

Section F Cold chain and transport

(fill up this section by asking and/or observing practice)

Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/No
○ If, "Yes", has there been any deviation outside of 2–8 ^{o}C after the vaccine was placed inside?	Yes/No
○ If, "Yes", provide details of monitoring separately:	
• Is the correct procedure of storing vaccines, diluents and syringes being followed?	Yes/No/UK
• Any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes/No/UK
• Are partially used reconstituted vaccines stored in the refrigerator?	Yes/No/UK
• Unusable vaccines (expired, no label, VVM stage 3 & 4, frozen) in the refrigerator?	Yes/No/UK
• Unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes/No/UK
Specific key findings/additional observations and comments:	
Vaccine transportation:	

• Type of vaccine carrier used	
• Vaccine carrier sent to the site on the same day of vaccination?	Yes/No/UK
• Vaccination carrier returned from the site on the same day of vaccination?	Yes/No/UK
• Conditioned ice pack used?	Yes/No/UK
Specific key findings/additional observations and comments:	

Section G Community investigation (please visit locality and interview parents/others)

Any similar events reported recently in the locality? Yes/No/UK
If "Yes", describe:

If "Yes", how many events/episodes?

Of those affected, how many are
- Vaccinated:_____
- Not Vaccinated:_____
- Unknown:_____

Other comments:

Section H Other findings/observations/comments

Section I District AEFI committee review & investigation report

a. Was the case discussed by the district AEFI committee? *If "Yes", then date case discussed by district AEFI committee*	Yes D D M M Y Y Y Y	No
b. *What was the provisional diagnosis of the case concluded by the district AEFI committee?*		
c. Did the district AEFI committee recommend that samples be sent for testing?	Yes	No

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
a) Any biological product (CSF, blood, urine) sent for testing? *If "Yes", specify details of the lab; attach copy of report if available* *Note: for AEFI resulting within 28 days following JE vaccine, send sample of CSF, serum to nearest NIV lab in Pune or Gorakhpur*							Yes	No
b) Was the local drug inspector involved in collecting additional samples?							Yes	No
c) Specify any other relevant investigation done and attach reports.								

Attached copies of reports/documents with this case investigation report:			
Ser No.	**List of document copies received**	**Availability** *(encircle)*	**Remarks (if any)**
1.	Case reporting form (CRF)	Yes/No	
2.	Post mortem report *(in case of death)*	Yes/No	
3.	Verbal autopsy form (in case of sudden unexplained death)	Yes/No	
4.	**Any pathology/microbiology test report**		
4A	Blood test report	Yes/No	
4B	CSF report	Yes/No	
4C	Urine test report	Yes/No	
5.	Doctor's prescription/treatment record for AEFI	Yes/No	
6.	Doctor's prescription/treatment record for other illness	Yes/No	
7.	Laboratory result of vaccine (if sent for testing)	Yes/No	
8.	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
9.	Any other document relevant to case	Yes/No	

District AEFI committee that conducted the investigation			
Name	**Designation**	**Phone #**	**Signature**
1.			
2.			
3.			
4.			

5.			
6.			
7.			

Section J **DIO/district nodal person** ***(Officer forwarding this report)***

Name …… Designation……..…Date of submission to state/national level……

Mobile No……..……. Landline (with STD code)……..…… Fax No. ……

email id……. Complete office address (with Pin code)……

……..…

……Signature and seal……. Date……

Please ensure that this preliminary investigation form reaches within 10 days of notification to:
1.State Immunization Officer
2. Deputy commissioner, Immunization Division of Govt. of India, MoHFW, Nirman Bhawan, New Delhi–110108.
(Fax: 011 23062728. email: **aefiindia@gmail.com**)

Annexure 3

FINAL CASE INVESTIGATION FORM

AEFI reporting ID: IND (AEFI) /__ST_/DIS_/_YR _/_NUM_ (To be allotted by DIO)

Section A

State	**District**
Block/ward	**Village/urban area**
Place of vaccination: Govt health facility/outreach/private health facility/other ____ **Session**: Routine (including SIW) Campaign (SIA)-IPPI/MR/JE/others (specify):_____ Other _____	
Name of investigator:	Date case visited and investigated: __ __/__ __/__ __ __ __
Posted at: Designation:	Date of preparing this form:__ __/__ __/__ __ __ __ Time of preparing this form: _____ a.m./p.m. This report is ☐ Preliminary ☐ Final
Contact phone number: email:	

Patient's name																		

Date of birth DD/MM/YYYY	Age (in months): _____ months	Sex	Male / Female

Mother's name																		
Father's name																		

Complete address of the case with landmarks *(street name, house number, village, block, tehsil, Pin no., telephone no.)*

P	**i**	**n**	-							**P**	**h**	**o**	**n**	**e**	-												

Attached copies of reports/documents with the final case investigation report:

Sl	List of document copies received	Availability *(encircle)*	Remarks (if any)
1	Case reporting form (CRF)	Yes/No	
2.	Preliminary case investigation form	Yes/No	
3	Any pathology/microbiology test report		
3a	Blood test report	Yes/No	
3b	CSF report	Yes/No	
3c	Urine test report	Yes/No	
4	Doctor's prescription/treatment record for AEFI	Yes/No	
5	Doctor's prescription/treatment record for other illness	Yes/No	
6	Laboratory result of vaccine (if sent for testing)	Yes/No	
7	Verbal autopsy form (in case of reported sudden unexplained death)	Yes/ No	
8	Post mortem report (based on guidelines for autopsy in case of reported unexplained death)	Yes/No	
9	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
10	Any other document relevant to case	Yes/No	

Date of Vaccination: __ __/__ __/__ __ __ __ Time of Vaccination: __ __: __ __ a.m./p.m.	Address of session site:
Date first notified to government health system: __ __/__ __/__ __ __ __	Notified by (please circle): Health worker/government doctor/private doctor/community/media/others (specify) _____

Date of first symptom	D	D	M	M	Y	Y	Y	Y	Time of first symptom	H	H	M	M	a.m.	p.m.	
Date of key symptom	D	D	M	M	Y	Y	Y	Y	Time of key symptom	H	H	M	M	a.m.	p.m.	
Hospitalization No/Yes – Date	D	D	M	M	Y	Y	Y	Y	Time of hospitalization	H	H	M	M	a.m.	p.m.	

Name and address of hospital (if hospitalized):

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	a.m.		p.m.			
Postmortem done? YES/No/Unknown If yes, then give date postmortem done	D	D	M	M	Y	Y	Y	Y	If not done, but planned, give date planned	H	H	M	M	Y	Y	Y	Y		

SECTION B: Refer to CRF, PCIF and updated information available for writing the case summary. Remember to include the following points, add additional sheet as necessary

Relevant information prior to immunization:

Status of immunization on the day AEFI reported (completed doses before the event):

Vaccines administered on the day of the event:

Post immunization event:

Examination findings:
Laboratory findings:
Details of community investigation, if conducted:
Any other findings:
Treatment provided:
Post mortem report if available:
Provisional diagnosis:

Add additional pages if needed

SECTION C:

Report of vaccine/diluent samples sent to CDL Kasauli as per details mentioned below

Vaccine/diluent name	Used vial/amp quantity	Batch No, lot No, date of expiry	Date sent	Lab finding	Unused vial/amp quantity	Batch No, lot No, date of expiry	Date sent	Lab finding

Report of syringe/needle samples sent to CDL Kolkata as per details mentioned below

Type of Syringes	Quantity	Batch No, Lot No, date of expiry	Date Sent	Lab finding	Type of needles	Quantity	Batch No, Lot No, date of expiry	Date Sent	Lab finding

Any biological product (CSF, blood, urine) sent for testing? *If yes, specify details of the lab; attach copy of report if available* *Note: For AEFI resulting within 28 days following JE vaccine, send sample of CSF, serum to nearest NIV lab in Pune or Gorakhpur.*	Yes	No	**Lab finding**
Specify any other relevant investigations done and attach reports			

District AEFI committee meeting when case was discussed

Name	Designation	Phone #	Signature
1.			
2.			
3.			
4.			
5.			
6.			
7.			

Section D **DIO/district nodal person** ***(Officer forwarding this report)***

Name ……. Designation……..…Date of submission to state/national level……

Mobile No……..……. Landline (with STD code)……..…… Fax No. ……

email id……. Complete office address (with Pin code)……

……

……Signature and seal……. Date……

Please ensure that this investigation form reaches within 70 days of notification to:

1.State Immunization Officer

2. Deputy commissioner, Immunization Division of Govt of India, MoHFW, Nirman Bhawan, New Delhi – 110108. (Fax: 011 23062728. email: aefiindia@gmail.com)

Annexure 4

AEFI – LABORATORY REQUESITION FORM (LRF)
(To be completed by drug inspector/DIO. LRF should be accompanied with specimens)

AEFI category (encircle): **Death/hospitalized/cluster/disability/others(specify)**_____

State		**Case ID**	**IND (AEFI)/** *State code /District code /Year /Serial No.*
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	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*		Age (in months)				Sex	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*	*a.m.*	*p.m.*

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

c) For Biological product specimen: (CSF, blood, urine)

Name of AEFI Case:	**Case ID IND (AEFI)/***State Code/District Code/Year/Serial No.*

2. Test requested:
3. Preliminary clinical diagnosis (working hypotheses) 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 cold chain officer				
State EPI Officer				
District immunization officer (DIO)				
Others (specify)				

To be completed by lab officials after receiving the specimen

Date of receipt of specimen(s) at laboratory	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*
Name of person receiving specimen(s) at laboratory								

Condition of specimen(s) upon receipt at lab (*encircle*)	Good*	Poor	Unknown
Comments by pathologist, virologist or bacteriologist:			

Date specimen(s) 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 5

CAUSALITY ASSESSMENT REPORT

(Office of State Immunization Officer)

(State AEFI committee to complete causality assessment exercise and forward this report to GoI within 30 days of receipt of final CIF at the state)

SECTION A (Preparation for causality assessment)

Date of receipt of Final CIF from district at state	D	D	M	M	Y	Y	Y	Y

Patient's name*																						
* Use separate form for each case in a cluster																						
Date of birth	D	D	M	M	Y	Y	Y	Y	**Age** (in months)			**Sex**	Male	Female								
Complete residential address of the case with landmarks *(Street name, house number, village, block, Tehsil, PIN No. etc.)*																						
P	**i**	**n**	-							**P**	**h**	**o**	**n**	**e**								

Check list for state EPI officer:

Sl. No.	List of document copies received	Availability *(encircle)*	Remarks (if any)
1.	Case reporting form (CRF)	Yes/No	
2.	Preliminary case investigation form	Yes/No	
3.	Postmortem report *(in case of death)*	Yes/No	
4	Verbal autopsy form (in case of sudden unexplained death)	Yes/No	
5	**Any pathology/microbiology test report**		
5A.	Blood test report	Yes/No	
5B.	CSF report	Yes/No	
5C.	Urine test report	Yes/No	
6.	Doctor's prescription/treatment record for AEFI	Yes/No	
7.	Doctor's prescription/treatment record for other illness	Yes/No	
8.	Laboratory result of vaccine (if sent for testing)	Yes/No	
9.	Laboratory result of syringes/other drugs (if sent for testing)	Yes/No	
10..	Any other document relevant to case	Yes/No	

Step 1 (Eligibility)

Name of the Parient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine / vaccination caused _____? (The event for review in step 2)

Has the _____ vaccine / vaccination caused _____?

Examples of causality questions

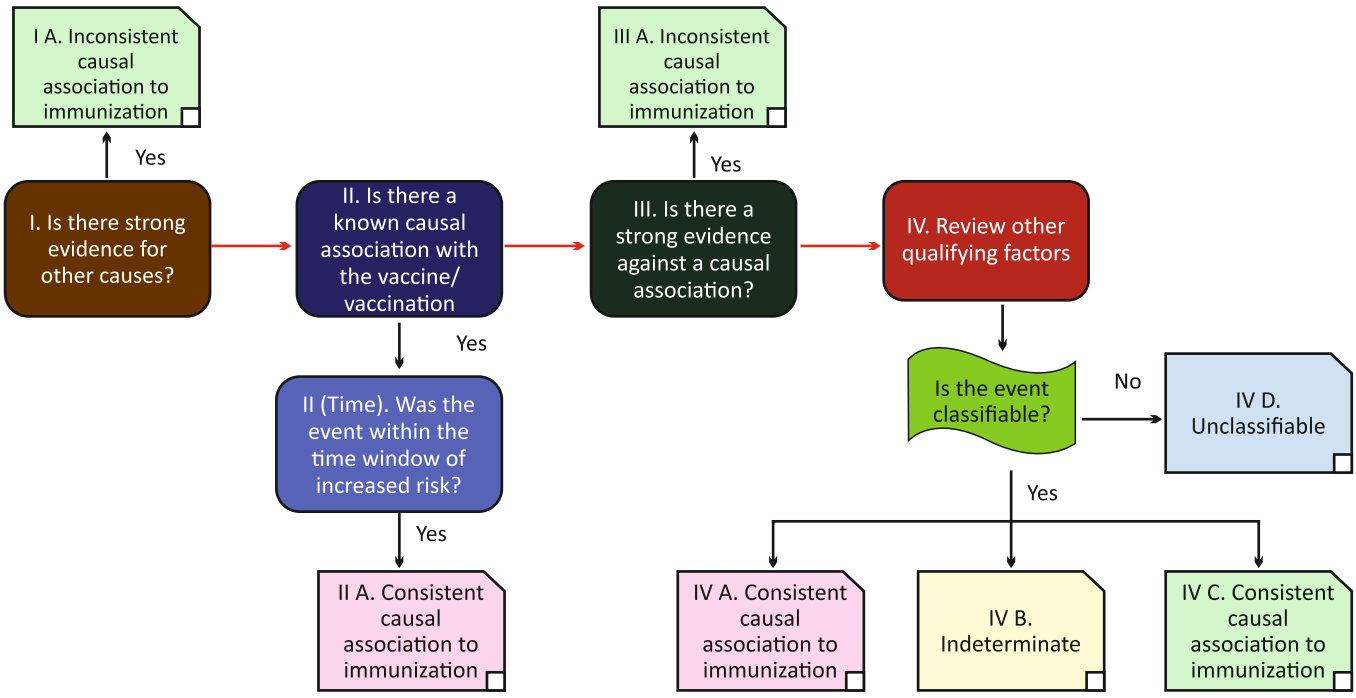
- "Has the vaccine A caused hepatomegaly?" (Anexample of an unfavorable or unintendedor unintended sign)
- "Has the vaccine B caused thrombocytopenia?" (An example of a laboratory finding)
- "Has the patient complained that the vaccine C caused itching and redness?" (An example of a symptom)
- "Has the vaccine D caused meningitis?" (An example of a disease).
- Imp: 'Death' is not a valid diagnosis. The pre-existing conditions or the circumstances leading to death should ne mentioned as a valid diagnosis

Step 2 (Event checklist)

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable

I. Is there strong evidence for other causes?	Y	N	UK	NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	☐	☐	☐	☐	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	☐	☐	☐	☐	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	☐	☐	☐	☐	
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (use beyond the expiry date, wrong recipient, etc.)?	☐	☐	☐	☐	
Was the vaccine (or any of its ingredients) administered unsterile?	☐	☐	☐	☐	
Was the vaccine's physical condition (colour, turbidity, presence of foreign substances) abnormal at the time of administration?	☐	☐	☐	☐	
Was there an error in vaccine constitution/preparation by the vaccinator (wrong product, wrong diluent, improper mixing, improper syringe filling)?	☐	☐	☐	☐	
Was there an error in vaccine handling (a break in the cold chain during transport, storage and/or immunization session)?	☐	☐	☐	☐	
Was the vaccine administered incorrectly (wrong dose, site or route of administration; wrong needle size)?	☐	☐	☐	☐	
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (vasovagal, hyperventilation or stress-related disorder)?	☐	☐	☐	☐	
II (time). If "Yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	☐	☐	☐	☐	
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	☐	☐	☐	☐	
IV. Other qualifying factors for classification					
Could the event occur independently of vaccination (background rate)?	☐	☐	☐	☐	
Could the event be a manifestation of another health condition?	☐	☐	☐	☐	
Did a comparable event occur after a previous dose of a similar vaccine?	☐	☐	☐	☐	
Was there exposure to a potential risk factor or toxin prior to the event?	☐	☐	☐	☐	
Was there acute illness prior to the event?	☐	☐	☐	☐	
Did the event occur in the past independently of vaccination?	☐	☐	☐	☐	
Was the patient taking any medication prior to vaccination?	☐	☐	☐	☐	
Is there a biological plausibility that the vaccine could cause the event?	☐	☐	☐	☐	

Step 3 (Algorithm) Review all steps and (✓) in all appropriate boxes



Notes for Step 3:

Step 4 (Classification) ✓ all boxes that apply

Check ✓ all boxes that apply

Adequate information availble

A. Consistent 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

B. Indeterminate

- ☐ B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (May be new vaccine-linked event)
- ☐ B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent causal association to immunization

- ☐ C. Coincidental

  Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

Adequate information not availble

☐ **Unclassifiable**

Specify the additional information required for classification

* "B1: This is a potential signal and maybe considered for investigation

Summarize the classification logic:
With available evidence, we could conclude that the classification is _____ because:

Details of state AEFI committee members who conducted the causality assessment			
Name	***Designation***	***Phone #***	***Signature***
1.			
2.			
3.			
4.			
5.			
6.			
7.			

Date of review of this case	D	D	M	M	Y	Y	Y	Y	Date of submission of report to GoI								

State nodal person (officer forwarding this report)

Name …… Designation……..…Date of submission to national level……

Mobile No……..…….. Landline (with STD code)…….…… Fax No. ……

Email id…… Complete Office address (with Pin code)…….

…….

…….

Signature/seal……..Date……..

Please ensure that this causality assessment report reaches:

Deputy Commissioner,
Immunization Division of Govt of India, MoHFW, Nirman Bhawan,
New Delhi – 110108.
(Fax: 011 23062728 email: aefiindia@gmail.com)

Section B ***For use at national level (Office of Deputy Commissioner- UIP)***								
Date of receipt of final CIF from district at national level	D	D	M	M	Y	Y	Y	Y
Date of receipt of causality assessment report from state	D	D	M	M	Y	Y	Y	Y

Annexure 6

District level line listing of reported AEFI cases

Year: _____

State		**District**	

Name of patient	AEFI case Epid no	Village/town/city	Date of birth	Date of immunization (dd/mm/yyyy)	Time of immunization	Date of onset	Time of onset	Date of notification by health worker/others	Date of case visit by MO	Date of reporting form (CRF) submission to the District by MO	Date of submission of CRF to the state/national level	Case Investigated by District? Yes/No (If yes, o investigation)	Date CIF(prelim) sent to State & Centre (write NA if not applicable)	Date CIF(final) sent to State & Centre (write NA if not applicable)	Clinical diagnosis	Reaction type (code) [1] Minor [2]Severe (3)Serious	Name of vaccines administered				Date of completion of causality assessment by the state	Cause (code) – to be assigned by the state AEFI committee	Remarks (other vaccines given) and documents sent to state with case investigation form
																	Vaccine1	Vaccine 2	Vaccine 3	Vaccine 4			
A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**				**S**	**T**	**U**

Coding for cause of AEFI:

[A1] Vaccine-product related	[A2] Vaccine quality defect related	[A3] Immunization-error related	[A4] Immunization anxiety related	[B1] Indeterminate – temporally related but insufficient definitive evidence	[B2] Indeterminate – conflicting trends of consistency and inconsistency	[C] Coincidental	[UC] Unclassifiable

Annexure 7

State level line listing of reported AEFI cases

Year: _____

State	

Name of the district	Name of patient	AEFI case Epid no	Village/town/city	Date of birth	Date of immunization (dd/mm/yyyy)	Time of immunization	Date of onset	Time of onset	Date of notification by health worker/others	Date of case visit by MO	Date of reporting form (CRF) submission to the District by MO	Date of submission of CRF to the state/national level	Case Investigated by District? Yes/No (If yes, date of investigation)	Date CIF(prelim) sent to State & Centre (write NA if not applicable)	Date CIF(final) sent to State & Centre (write NA if not applicable)	Clinical diagnosis	Reaction type (code) [1] Minor [2]Severe (3)Serious	Name of vaccines administered				Date of completion of causality assessment by the state	Cause (code)- to be assigned by the state AEFI committee	Remarks (, documents sent to state with Case investigation form . other vaccines given etc)
																		Vaccine1	Vaccine 2	Vaccine 3	Vaccine 4			
X	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**				**S**	**T**	**U**

Coding for cause of AEFI:

(A1) Vaccine-product related	[A2] Vaccine quality defect related	[A3] Immunization-error related	[A4] Immunization anxiety related	[B1] Indeterminate – temporally related but insufficient definitive evidence	[B2] Indeterminate – conflicting trends of consistency and inconsistency	[C] Coincidental	[UC] Unclassifiable

Annexure 8

National level line listing of reported AEFI cases

Year: _____

Country	

Name of the state	Name of the district	Name of Patient	AEFI case Epid no	Village/town/city	Date of birth	Date of immunization (dd/mm/yyyy)	Time of immunization	Date of onset	Time of onset	Date of notification by health worker/others	Date of case visit by MO	Date of reporting form (CRF) submission to the district by MO	Date of submission of CRF to the state/national level	Case investigated by district? Yes/No (If yes, date of investigation)	Date CIF(prelim) sent to State & Centre (write NA if not applicable)	Date CIF(final) sent to State & Centre (write NA if not applicable)	Clinical diagnosis	Reaction type (code) [1] Minor [2]Severe (3)Serious	Name of vaccines administered				Date of completion of causality assessment by the state	Cause (code) – to be assigned by the state AEFI committee	Remarks (, documents sent to state with Case investigation form . other vaccines given etc)
																			Vaccine1	Vaccine 2	Vaccine 3	Vaccine 4			
XX	**X**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**				**S**	**T**	**U**

Coding for cause of AEFI:

(A1] Vaccine-product related	[A2] Vaccine quality-defect related	[A3] Immunization-error related	[A4] Immunization anxiety related	[B1] Indeterminate – temporally related but insufficient definitive evidence	[B2] Indeterminate – conflicting trends of consistency and inconsistency	[C] Coincidental	[UC] Unclassifiable

Annexure 9

Suggested format for block AEFI register

Week No	Name of sub-centre	Name of vaccinee	Father's name	Age	Date of vaccination	Name of vaccines given	AEFI noted (symptoms)	Category (serious/ severe/ minor)	Case seen by MO i/c (Yes/No)	Entered in case reporting form (Yes/No)

1. Kindly follow the AFP surveillance calendar to identify week No.
2. Information on serious and severe AEFI should be shared weekly with the district along with the H-002 form
3. The details of minor AEFI are to be maintained at block Level and monthly cumulative data to be entered in HMIS report.

Annexure 10

AEFI case definitions and treatment

Adverse event	Case definition	Treatment	Vaccines
Acute flaccid paralysis (AFP)	• Acute onset of flaccid paralysis within 4 to 30 days of receipt of OPV, or within 4 to 75 days after contact with a vaccine recipient • neurological deficits remaining 60 days after onset; or • death	No specific treatment available; supportive care	Oral polio vaccine (OPV)
Anaphylactic reaction (acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more the following: • wheezing and shortness of breath due to bronchospasm • one or more skin manifestations, e.g. hives, facial oedema, or generalized oedema. Less severe allergic reactions do not need to be reported • laryngospasm, laryngeal oedema	Self-limiting; anti-histamines may be helpful	All
Anaphylaxis	Severe and immediate allergic reaction (within 1 hour) leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema	Adrenaline injection	All
Arthralgia	Joint pain, usually including the small peripheral joints. Persistent if lasting longer than 10 days; transient if lasting up to 10 days	Self-limiting; analgesics	Rubella; MMR

Adverse event	Case definition	Treatment	Vaccines
Brachial neuritis	• Dysfunction of nerves supplying the arm/shoulder without any other involvement of the nervous system • A deep, steady, often severe aching pain in the shoulder and upper arm, followed in days or weeks by weakness and wasting in arm/shoulder muscles • Sensory loss may be present, but is less prominent. May present on the same or the opposite side to the injections and sometimes affects both arms	Symptomatic only; analgesics	Tetanus
Disseminated BCG infections	Widespread infections occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of mycobacterium bovis BCG strain. Usually in immunocompromised individuals	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin	BCG
Encephalopathy	Acute onset of major illness characterized by any two of the following three conditions: • Seizures • Severe alteration in level of consciousness lasting for one day or more • Distinct change in behavior lasting one day or more Needs to occur within 48 hours of DTP vaccine or from 7 to 12 days after measles or MMR vaccine to be related to immunization	No specific treatment available; supportive care.	Measles, pertussis
Fever	The fever can be classified (based on rectal temperature) as • Mild: 100.4 to 102 °F (38 to 38.9 °C), • High: >102 °F to 104.7 °F (39 to 40.4 °C) and • Extreme: 104.8 °F or higher (40.5 °C or higher). High/extreme fever should be reported.	Symptomatic; paracetamol	All

Adverse event	Case definition	Treatment	Vaccines
Hypotonic hyporesponsive episode (HHE) or shock-collapse	Event of sudden onset occurring within 48 (usually less than 12) hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • Limpness (hypotonic) • Reduced responsiveness (hyporesponsive) • Pallor or cyanosis, or failure to observe/recall	The episode is transient and self-limiting, and does not require specific treatment. It is not a contraindication to further doses of the vaccine	Mainly DTP, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (purulent, inflammatory signs, fever, culture); sterile abscess if not	Incise and drain; antibiotics if bacterial	All
Lymphadenitis (includes suppurative lymphadenitis)	• At least one lymph node enlarged to >1.5 cm in size (one adult finger width), or a draining sinus over a lymph node • Almost exclusively caused by BCG and occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary)	Heals spontaneously (over months) and best not to treat unless lesion is sticking to the skin. If so, or if already draining, surgical drainage and local instillation of anti-tuberculosis drug. Systemic treatment with anti-tuberculosis drugs is ineffective	BCG
Osteitis/osteomyelitis	Inflammation of the bone with isolation of mycobacterium bovis BCG strain	Should be treated with anti-tuberculosis regimens including isoniazid and rifampicin	BCG
Persistent inconsolable screaming	Inconsolable continuous crying lasting 3 hours or longer accompanied by high-pitched screaming	Settles within a day or so; analgesics may help	DTP, pertussis

Adverse event	Case definition	Treatment	Vaccines
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures if temperature elevated >100.4 °F (rectal); afebrile seizures if temperature normal	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants	All, especially pertussis, measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as possible indicator of immunization error	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids	All
Severe local reaction	Redness and/or swelling centered at the site of injection and one or more of the following: • Swelling beyond the nearest joint • Pain, redness, and swelling of more than 3 days duration Requires hospitalization. Local reactions of lesser intensity occur commonly; these are trivial and do not need to be reported	Settles spontaneously within a few days to a week. Symptomatic treatment with analgesics. Antibiotics are inappropriate	All
Thrombocytopaenia	Serum platelet count of less than 50 000/ml leading to bruising and/or bleeding	Usually mild and self-limiting; occasionally, may need steroid or platelets	MMR
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours. Needs to be reported as possible indicator of immunization error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids	All

Brighton Collaboration has developed case definitions for many vaccines reactions that are available at www.brightoncollaboration.org.

Annexure 11

Frequency of vaccine adverse reactions of commonly used vaccines

BCG vaccine summary	
Vaccine adverse reactions	**Frequency category**
▪ Injection site reaction (papule, mild ulceration or scar)	Very common
▪ Supportive lymphadenitis	Uncommon to rare
▪ BCG osteitis	Uncommon to very rare
▪ Disseminated BCG disease or systemic BCGitis	Very rare
▪ Immune reconstitution inflammatory syndrome (IRIS)	Very rare

Hepatitis B vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Fever	Common
▪ Headache	Common
▪ Injection site pain	Common to very common
▪ Injection site redness	Common
▪ Injection site swelling	Common
▪ Anaphylaxis	Very rare

DTP vaccines summary	
Vaccine adverse reactions	**Frequency category**
Whole cell pertussis vaccines	
▪ Fever 100.1–102 °F	Very common
▪ Injection site redness	Very common
▪ Swelling	Very common
▪ Pain (severe–moderate)	Very common
▪ Fussiness (severe-moderate)	Very common
▪ Drowsiness	Very common
▪ Anorexia	Very common
▪ Vomiting	Common
▪ Persistent screaming	Uncommon to Rare
▪ HHE	Very rare
▪ Seizures	Very rare
▪ Encephalopathy	Very rare
▪ Anaphylaxis	Very rare
Acellullar pertussis vaccines	
▪ Fever 100.1–101 °F	Very common
▪ Fever 100.1–102 °F	Common
▪ Injection site redness	Common to very common
▪ Injection site swelling	Common to very common
▪ Pain (severe–moderate)	Uncommon to common
▪ Fussiness severe–	Common to very common
▪ Drowsiness	Very common
▪ Anorexia	Very common
▪ Vomiting	Very common
▪ Persistent screaming	Uncommon
▪ HHE	Rare
▪ Seizures	Very rare

Human papilloma vaccines (HPV) summary	
Vaccine adverse reactions	**Frequency category**
Bivalent HPV vaccine	
▪ Fever	Common
▪ Headache	Very common
▪ Injection site pain	Very common
▪ Redness	Very common
▪ Swelling	Very common
▪ Rash	Uncommon
▪ Arthralgia	Very common
▪ Myalgia	Very common
▪ Fatigue	Very common
▪ Gastrointestinal Disorders	Very common
Quadrivalent HPV vaccine	
▪ Fever	Very Common
▪ Headache	Very Common
▪ Injection site pain	Common
▪ Redness	Common
▪ Swelling	Common
▪ Urticaria	Common
▪ Arthralgia	Common
▪ Myalgia	Common
▪ Gastrointestinal Disorders	Very Common
▪ Anaphylaxis	Very Rare

Tetanus vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Brachial neuritis	Very rare
▪ Anaphylaxis	Very rare

Hib vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Fever	Common
▪ Injection site reaction	Very common

Polio vaccines summary	
Vaccine adverse reactions	**Frequency category**
Oral Polio Vaccine (OPV)	
▪ VAPP – Recipient VAPP – Total VAPP	Very rare Very rare
Inactivated Polio Vaccine (IPV)	
▪ Injection site erythema	Uncommon to common
▪ Injection site induration	Common to very common
▪ Injection site tenderness	Very common

Measles vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Fever	Common to very common
▪ Rash	Common
▪ Injection site reaction	Very common
▪ Febrile seizures	Rare
▪ Encephalomyelitis	Very rare
▪ Thrombocytopenia	Very rare
▪ Anaphylaxis	Very rare

Pneumococcal vaccines summary	
Vaccine adverse reactions	**Frequency category**
Unconjugated vaccine (PPSV)	
▪ Fever > 102.2 °F	Uncommon
▪ Injection site reaction	Very common
Conjugated vaccine (PCV)	
▪ Fever > 102.2 °F	Uncommon
▪ Injection site reaction	Very common

Rubella vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Fever	Common
▪ Injection site reaction	Very common
▪ Acute Arthralgia (adults)	Very common
▪ Acute Arthritis (adults)	Very common

Varicella vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Febrile seizures	Rare
▪ Fever > 102.2 °F	Very common
▪ Injection site reaction	Common to very common
▪ Site rash (local/generalized)	Common

Mumps vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Injection site reaction	Very common
▪ Parotid swelling	Common
▪ Aseptic meningitis	Very common

Rotavirus vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Intussusception	Very rare

Yellow fever vaccines summary	
Vaccine adverse reactions	**Frequency category**
▪ Vaccine-associated viscerotropic disease	Very rare

Key		
Very common	> 1/10	> 10%
Common	> 1/100 and < 1/10	> 1% and < 10%
Uncommon	> 1/1000 and < 1/100	> 0.1% and < 1 %
Rare	> 1/10 000 and < 1/1000	> 0.01% and < 0.1%
Very rare	< 1/10 000	< 0.01%

Annexure 12

Verbal autopsy form for interviewing family of reported AEFI

EPID NO……../……./…….

To be filled only in cases where inadequate information is available *(brought dead/home death/insufficient medical records/not hospitalized/clinical diagnosis not possible)

I would like to ask you some questions concerning signs and symptoms that the child/person had/showed prior to and/or at the time of event, previously known medical conditions the child/person had and injuries and accidents that the child/person 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 all possible conditions that the child/person had.

Section 1. Basic details

A) Patient identifiers

Name of the child/person: _____ _____ _____

Age (in months/years): Sex (Male/Female): Date of birth:

Complete address:

Phone No: Education:

Case number:_____

State:_____District :_____Block: _____Village:_____

Pin code:

Name of head of the household:_____ _____ _____

B) Details of respondent

Sr No	Details of respondent	Relation with deceased
1		
2		
3		
4		
5		
6		

Name of the main respondent:
Relation of main respondent with child /person:

Main respondent's age: Sex (Male/Female): Education:

Did the respondent live with the deceased during the events that led to death? (Yes/No)

Date & time of event:

Place at which event occurred: home/govt facility/private facility/others (please specify:_____

C) Details of current vaccination:

Date: Time: Place:

Vaccine(s) administered ……. Name: ……. Route: IM/SC/ID……Site:……

Vaccine name	Route (IM/SC/ID)	Site (verify site from mother)
Vaccine 1		
Vaccine 2		
Vaccine 3		
Vaccine 4		

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)

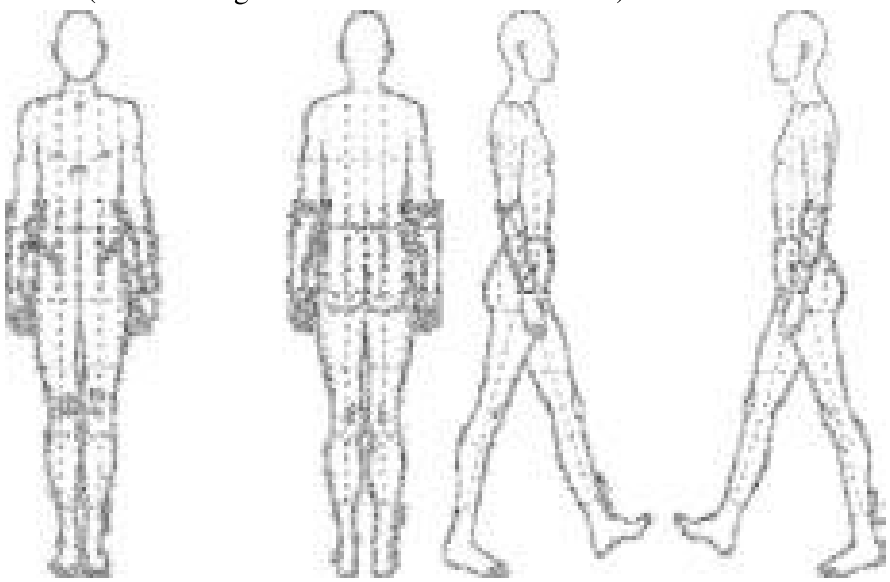
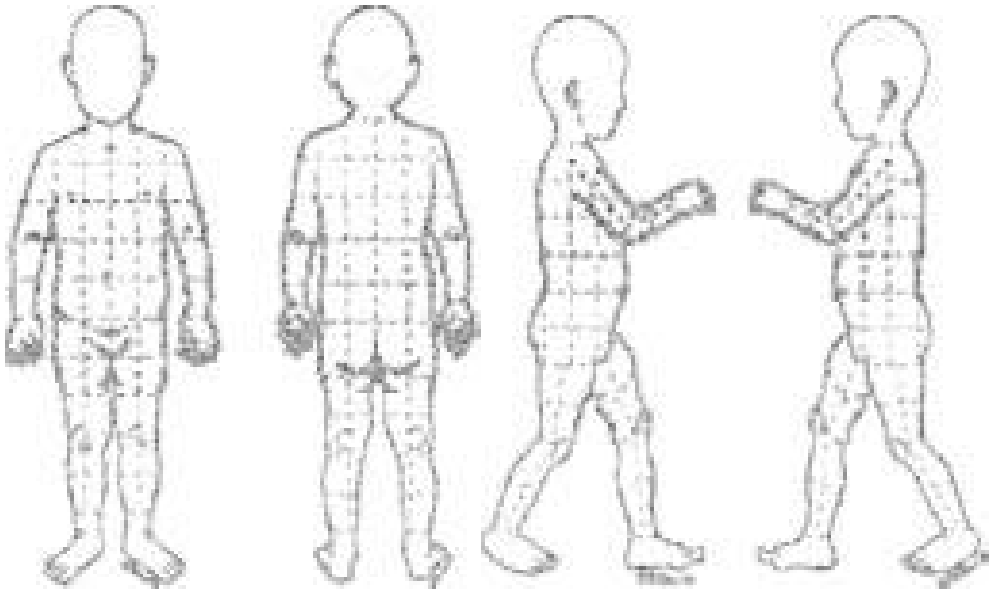


Fig. 2. Drawing of front, back, left side and right side of infant to mark injection sites with respective vaccines, location of swelling at or near injection site and position at time of death. (Source: Brighton collaborations definitions)



Who administered the
vaccine(s)ANM…LHV…..PHN….Pharmacist……Doctor……Others (specify) …..

D) Past history of the child/person:

Previous immunizations received: Collect immunization card, if available and check for card from AW or PHC

Reactions to previous vaccines Yes/No (If yes, specify_____)

History of previous allergy Yes/No (If yes, specify_____)

Seizures/holding breath/cyanosis Yes/No (If yes, specify_____)

Pre-existing illness……. Yes/No (If yes, specify_____)

History of hospitalization in last Yes/No (If yes, specify_____)

30 days with cause

E) Nutritional status:

Weight (in kgs): _____ Date when taken (dd/mm/yyyy) ___/___/_____
(Check immunization card/medical records)

F) Personal history (for adults)

H/o of systemic disorder: Diabetes/hypertension/asthma/epilepsy/AIDS/tuberculosis/any other medically diagnosed illness (please specify_____)

H/o any addiction: Tobacco/alcohol/other (specify) _____ Frequency:_____
Since how long: _____-____

Section 2. For cases of children (from 0 to 5 years)

If weight not available, ask whether the child looked weaker/smaller as compared to babies of similar age

Yes /No

A) Birth details (check records if available):

Birth weight:

Child's size, if weight is unknown (small/average/larger than average/unknown):

Place of delivery

Type of delivery (normal/caesarian/forceps)

Was s/he born premature? (A premature birth is one that is at least three weeks before a baby's due date. It is also known as preterm birth, i.e. less than 37 weeks. The full term is 40 weeks.)

Yes/No (If yes, please specify details_____)

Did s/he have any malformation at birth?

Yes/No (If yes, please specify details_____)

Were there any complications during pregnancy/at birth?

Yes/No (If yes, please specify details_____)

The infant was (single or multiple pregnancy)? Please

specify_____)

History of any birth defects?..... ……..

B) Feeding history:

Breast-fed (Yes/No)

Other foods Yes/No (If yes, specify_____)

What foods and liquids was the child fed in the past 24 hours? Include last feed.

Breast milk: Yes/No (If yes, frequency and when last fed _____)

Animal milk: Yes/No (If yes, frequency and when last fed _____)

Water: Yes/No (If yes, frequency and when last fed _____)

Other liquids (give details): Yes/No (If yes, frequency and when last fed_____)

Solids (give details): Yes/No (If yes, frequency and when last fed _____)

On what day and at what approximate time was the child last fed?

Date: Time:

Who last fed the child:

When was the last feed:

C) Medical conditions
What condition(s)did the child have? (see the options below)

Condition	Unknown	No	Yes	Specify time, order of appearance and treatment given by family
Fever				
Diarrhoea				
Excessive sweating				
Stool changes				
Lethargy or sleeping more than usual				
Fast/difficulty in breathing				
Fussiness or excessive crying				
Apnea (stopped breathing)				
Poor feeding				
Cyanosis (turned blue/grey)				
Vomiting				
Seizures or convulsions				
Skin rash/flushing				
Choking				

D) Development status:
Appropriate for age/delayed: If delayed, give details:
_____

E) In case of death at home:
Where was the child placed? _____

Where was the child last known to be alive? _____When?.....

In what position was the child last placed? (Sitting/on back/on side/on stomach/unknown)

In what position was the child found? (Sitting/on back/on side/on stomach/unknown)

Face position when last placed (Face down on surface/face up/face to a side)

Face position when child found (Face down on surface/face up/face to a side)

What was the child wearing? _____

What was the temperature in child's room? (Hot/cold/normal/other. Please specify _____)

Was anyone sleeping with the child? (Yes/No)

Which of the following items were within the child's reach?

(Toys/pillows/polythene bags/blankets/sheet/others. please 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 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)				
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 touching when found?
(Sweaty/warm to touch/cool to touch/limp/flexile/rigid/stiff/unknown/others. Please specify

_____

Did anyone try to revive the child? Yes/No (If yes, give details_____)

_____

Section 3: Treatment and health service use prior to event (specially for cases with insufficient medical records)

	Did the child/person receive any treatment for the event?	Yes /No
1	If yes, please list the treatments the child/person was given prior to and after the event. a) Oral _____ b) Injectable _____ c) Local application _____ *All medications should be verified by prescriptions, where possible*	
2	At which of the following places or facilities did the child/person receive treatment for the event? Home/traditional healer/government clinic/government hospital/private clinic/private hospital/pharmacy/drug seller/store/any other place or facility	

3	In the month before the event, how many contacts with formal health services did the child/person have?	
4	Did a health-care worker tell you the cause of the event ?	Yes/No
	Copy from prescription/discharge notes if available	
5	What did the health care worker say?	

Section 4: Respondent/witness interview

Did the respondent witness the events that led to event? (Yes/No)

If not, obtain the following details from the witness:

Witness name and relation to the child: _____

Are you the usual caregiver? Yes/No

Time of onset of symptoms after vaccination:

How was the injection site? (Normal/red or blue discolouration/swelling/any other.

Please specify_____)

Section 5: Family history

Number of people staying in the house and relation to the child /person:

Socioeconomic status:

Health status of siblings:

Consanguinity: Yes/No (If yes, specify_____)

Recent illness in family? Yes/No (If yes, specify_____)

Occupation of father/mother:

History of similar illness to any child in family:

Presence of adverse family circumstances:

(family relationships/economics/behavioral/addictions/circumstantial evidence): Yes/No

(If yes, specify_____)

Any other significant factor:

Tell me what happened (Record verbatim the narrative of the witness in his/her words):

Any other comments /observations about circumstances of the event…….

Section 6: Interviewer's observations* (Case summary)

(Emphasis should be placed on establishing the exact chronology of events from point of vaccination to occurrence of event)

Comments on specific questions/any other comments:

Section 7: Final diagnosis

Treatment given:

Attach copies of all available documents (including case sheets, discharge summary, laboratory reports and post mortem reports)
*(To be filled in after completing interview)

Name of interviewer:

Designation:

Address:

Contact no.:

email:

Fax:

Annexure 13

Central Drugs Standard Control Organization (CDSCO) offices and contact details in India

A. CDSCO (NORTH ZONE)

Address: C.G.O. Building-I, Kamla Nehru Nagar, Hapur Chungi, Ghaziabad–201 002 (U.P.).
Phone: Office-0120-2719483/2750013, 0120-2701927 (D). Fax: 0120-2719483.
Gram: *ZONDRUG-GHAZIABAD.* email: cdsconz@gmail.com.

Headed by Deputy Drugs Controller (India)

AEFI Cell i/c: Asst Drugs Controller (India)

States jurisdiction: Haryana, Himachal Pradesh, Jammu & Kashmir, Punjab, Rajasthan, Uttaranchal, Uttar Pradesh, NCT of Delhi & Union Territory of Chandigarh.

1. **SUBZONAL OFFICE (CHANDIGARH)**

   Headed by: Asst Drugs Controller (I), CDSCO Sub-zonal office, DGHS, MoHFW, Sector 39 C, Chandigarh–160036. Phone: 0172-2625633. email: cdscocdg@gmail.com.

2. **SUBZONAL OFFICE (JAMMU & KASHMIR)**
   Headed By: Asst Drugs Controller (I), CDSCO Sub-zonal office , Controller of Drugs & Food Organisation, Patoli Mangotrian, P.O. Janipur, Jammu–180007. Phone: 0191-259883; email:cdscojsz@gmail.com.

B. EAST ZONE

Headed by: **Deputy Drugs Controller (I),** Central Drugs Standard Control Organisation, East Zone, C.G.O. Bldgs., (Nizam Palace) West, Second Floor, 234/4, Lower Circular Road, Kolkata–700 020. Phone: Office 033-22870513/22801391. Gram: *ZONDRUG- KOLKATA.* Fax: 033-22813806. email: cdscoez@gmail.com.

AEFI Cell i/c: Asst Drugs Controllers (India)

States jurisdiction: Andaman and Nicobar Islands, Arunachal Pradesh, Assam, Bihar, Jharkhand, Manipur, Meghalaya, Mizoram, Nagaland, Orissa, Sikkim, Tripura & West Bengal.

C. CDSCO (WEST ZONE)

Headed By: Deputy Drugs Controller, DDC(I), Central Drugs Standards Control Organization, West Zone, Fourth Floor, Zonal FDA Bhawan, GMSD Compound, Bellasis Road, Mumbai Central, Mumbai–400 008. Phones: 91-22- 23002279, 23002215, 23092971. Fax: 91 (22) 23002271 Resi. 91-22-27823483. email: cdscowz@gmail.com , ddciwzmum-mohfw@nic.in.

AEFI Cell i/c: Assistant Drugs Controller (India)

States jurisdiction: Chattisgarh, Goa, Daman & Diu, Madhya Pradesh and Maharashtra.

1. **SUBZONAL OFFICE (GOA)**
   Headed By: Assistant Drugs Controller (India), Central Drugs Standard Control Organization Sub zonal office, Third Floor, Customs Building, Custom House, Marmagoa, Goa–403803. Phone: 0832-2520341. Fax: 0832-2522094/2520176. email:cdscogoa@gmail.com.

2. **SUBZONAL OFFICE (INDORE)**
   Headed By: Assistant Drugs Controller (India), Central Drugs Standard Control Orgnization, Sub zonal Indore C/o Container Corporation of India Ltd, Inland Container Depot, 113, Concor Complex, Sector-3, Pithampur Industrial Area, Pithampur, Dist. Dhar, Madhya Pradesh. email:gautam.parag29@gmail.com.

D. AHMEDABAD ZONAL OFFICE

Headed by: Deputy Drugs Controller (I), Zonal Office, Ahmedabad, Central Drug Standards Control Organization, Old Terminal Building, Air Cargo Complex, Airport, Ahmedabad-380 003. Tele Fax: 079-22865244, 22850706, 22850707.

State jurisdiction: Gujarat

E. SOUTH ZONE

Headed By: Deputy Drugs Controller (I), Central Drug Standard Control Organisation, South Zone, Second Floor, Shastri Bhawan, Annexe, 26, Haddows Road, Chennai–600 006. Phone: Off. 044 - 28278186.

AEFI Cell in-Charge: Asst Drugs Controller (I), Port, Room No. 23, IV Floor, Annexe Bldg, Custom House, Chennai–600 001. Phone: Off: 5212041. Gram: DRUGCONIND.

States jurisdiction: Karnataka, Kerala, Pondicherry and Tamil Nadu

F. HYDERABAD ZONAL OFFICE

Headed by: Deputy Drugs Controller (India), CDSCO, Zonal office, Hyderabad, CDSCO BHAVAN, Beside T.B. & Demonstration Centre, S.R. Nagar, Hyderabad–500038, AP. Phone: 040-23811481. TeleFax: 040-23811483,
email: ddchyderabad@gmail.com,cdscohyd@gmail.com.

Annexure 14

WHO National Regulatory Authority (NRA) assessment indicators for vaccine pharmacovigilance function

NRA indicators assessing pharmacovigilance including AEFI surveillance

	Indicator	Critical status
PV01	Institutional regulations and guidelines for the monitoring and management of AEFI	Critical
	PV01.01: Legal provisions for pharmacovigilance exist in the public and/or private sectors as appropriate.	Critical
	PV01.02: Guidelines exist, are published and accessible, are distributed and/or are available when needed to all staff involved in AEFI surveillance, and are actively used.	Critical
	PV01.03: Provisions for the NRA to require the marketing authorization holder to perform a specific study of safety in the post-marketing period as necessary.	Critical
	PV01.04: Requirements exist for the manufacturer to inform the NRA of any new safety signal or marketing regulatory decisions taken in other countries based on safety and is enforced by NRA.	Critical
PV02	Quality management system for pharmacovigilance activities	Critical
	PV02.02: Defined organizational chart and responsibilities to implement the quality management system	Critical
	PV02.02: Management system to ensure traceability of actions	Critical
	PV02.03: Auditing system documented and implemented (external and internal)	Not critical
PV03	Human resource management	Critical
	PV03.01: Adequate qualified staff (numbers, education, training, skills and experience) to perform pharmacovigilance activities	Critical
	PV03.02: Staff training plan developed but not implemented	Not critical
	PV03.03: Monitoring of acquired skills and/or competencies of the staff after training.	Not critical

	Indicator	Critical status
PVO4	Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action	Critical
	PVO4.01: AEFI data compiled and analyzed/interpreted on a regular (e.g. monthly) basis	Critical
	PVO4.02: Information on serious cases, AEFI clusters and investigation reports shared between NRA, National Control Laboratory (NCL), national immunization programme and disease surveillance and pharmacovigilance staff	Critical
	PVO4.03: Formal/official communication and regular meetings among above-mentioned key players when dealing with AEFI	Not critical
	PVO4.04: Availability of an expert committee to review serious AEFI cases and performance of the national PV system	Critical
	PVO4.05: Manufacturers are notified of significant safety and efficacy issues and kept up to date or/and at upon request	Not critical
	PVO4.06: Process to review/assess AEFI and initiate appropriate action including at the sub-national level, when needed	Not critical
	PVO4.07: Inclusion of "zero" events in routine periodic reports	Not critical
PV05	Capacity to detect and investigate significant vaccine safety issues	Critical
	PV05.01: Demonstrated capacity of the reporting system (active or passive, sentinel or countrywide/statewide) with satisfactory sensitivity	Critical
	PV05.02: Documented evidence of appropriate investigations or sufficient elements indicative of capacity to investigate	Critical
	PV05.03: Evidence of timely reporting and investigations is documented.	Critical
	PV05.04: A national database or system for collating, managing and retrieving AEFI reports exists.	Critical

	Indicator	Critical status
PV06	Regulatory actions regarding vaccine performance	Critical
	PV06.01: Evidence that appropriate regulatory action consistent with NRA guidelines is taken in serious AEFI cases.	Critical
	PV06.02: NRA regularly informed of data relevant to ongoing assessment of vaccine performance	Critical
PV07	Communication system is in place to periodically inform stakeholders about AEFI information.	Not critical
	PV07.01: Periodic (quarterly or yearly) feedback on AEFI, including summary and specific investigation reports	Not critical
	PV07 02: Process is established for feedback down to health facility level.	Not critical
	PV07.03: Process is established for feedback to public/community/patients/parents.	Not critical

Annex 15

Websites on vaccine safety

Brighton Collaboration	www.brightoncollaboration.org
Centers for Disease Control and Prevention (CDC), USA	www.cdc.gov/nip/vacsafe www.cdc.gov/vaccinesafety/Activities/VSD.html http://www.cdc.gov/vaccines/recs/acip/default.htm
Chinese Centre for Disease Control and Prevention	http:/www.chinacdc.cn/en/
Council for International Organizations of Medical Sciences (CIOMS)	http://www.cioms.ch/
Department of Health, UK	http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/
World Health Organization	www.who.int/gpv-safety www.who.int/immunization/sage/en http://www.who.int/vaccine_safety/en/ http://www.wpro.who.int/health_topics/immunization/
WHO Global Vaccine Safety Resource Centre (GVS RC)	http:/www.who.int/entity/vaccine_safety/initiative/tech_support/en/index.html
WHO E-learning course on Vaccine Safety Basics	www.vaccine-safety-training.org
Aide-memoire on investigation causality assessment	http://www.who.int/vaccine_safety/en/
WHO vaccine reaction rates information sheets	http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html

Annexure 16

Recognition and treatment of anaphylaxis

Anaphylaxis is a very rare, unexpected and occasionally fatal allergic reaction. It is reported even more rarely from developing countries. In addition, misdiagnosis of faints and other common causes of collapse as anaphylaxis can lead to inappropriate use of adrenaline. Vaccinators should be able to distinguish anaphylaxis from fainting (vasovagal syncope), anxiety and breath-holding spells, which are common benign reactions.

During fainting, the individual suddenly becomes pale, loses consciousness and collapses to the ground. Fainting is sometimes accompanied by brief clonic seizure activity (i.e. rhythmic jerking of the limbs), but this requires no specific treatment or investigation. Fainting is relatively common after immunization of adults and adolescents, but very rare in young children. 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.

An anxiety spell can lead to pale, fearful appearance and symptoms of hyperventilation (lightheadedness, dizziness, tingling in the hands and around the mouth). Breath-holding occurs in young children and will lead to facial flushing and cyanosis. It can end in unconsciousness, during which breathing resumes. Anaphylaxis develops over several minutes up to a few hours and usually involves multiple body systems. Unconsciousness is rarely the sole manifestation of anaphylaxis; it only occurs as a late event in severe cases. A strong central pulse (e.g. carotid) is maintained during a faint, but not in anaphylaxis.

Difference between a fainting attack and anaphylaxis

Clinical features	Fainting	Anaphylaxis
Timing	Before, during or few minutes after injection	A short time, up to a few hours
Skin	Generalized pallor, cold and clammy skin	Itching, generalized erythema, urticaria, swelling of lips, face, tingling around lips
Respiratory system	Normal breathing, shallow breathing	Tachypnoea, difficulty in breathing, wheezing, stridor, hoarseness, cyanosis, recession of intercostal spaces
Cardiovascular	Bradycardia, weak pulse, carotid pulse felt, hypotension may occur – reversed by supine position	Tachycardia, weak pulse, carotid pulse may be weak, hypotension – not reversed by supine position
GIT	Vomiting	Vomiting, diarrhoea, abdominal cramps
CNS	Faintness, light-headedness relieved by supine posture	Anxiety and distress, loss of consciousness not relieved by supine posture

Panic attack – no hypertension, pallor, wheeze, urticarial rash or swelling. May have flushing or blotchy skin.

Before immunization, check for contraindications to immunization by asking about known allergies and previous adverse reactions to vaccines. In cases of possible serious allergies, check with a specialist before giving the vaccine.

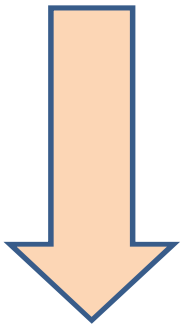
Recognition

Anaphylaxis is a severe reaction of rapid onset, characterized by circulatory collapse. The early signs of anaphylaxis are generalized erythema and urticaria with upper and/or lower respiratory tract obstruction. In more severe cases, limpness, pallor, loss of consciousness and hypotension may also become evident. Vaccinators should be able to recognize the signs and symptoms of anaphylaxis given below.

Diagnostic features of anaphylaxis

Respiratory	Airway • Throat and tongue swelling (pharyngeal/laryngeal oedema) – the patient has difficulty in breathing and swallowing and feels that the throat is closing up • Hoarse voice • Stridor Breathing • Bronchospasm • Respiratory distress – two or more of the following: - Tachypnoea - Increased use of accessory respiratory muscles - Recession - Cyanosis • Grunting • Respiratory arrest
Cardiovascular	• Hypotension • Clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following: - Tachycardia - Capillary refill time >3 s - Reduced central pulse volume - Decreased level of consciousness or loss of consciousness • Cardiac arrest • Bradycardia (a slow pulse) is usually a late feature, often preceding cardiac arrest
CNS	• Confusion/agitation • Headache • Loss of consciousness

Diagnostic features of anaphylaxis	
Dermatologic or mucosal	• Tingling of lips • Generalized urticarial or generalized erythema • Angioedema, localized or generalized (angioedema is similar to urticaria but involves swelling of deeper tissues, most commonly in the eyelids and lips, and sometimes in the mouth and throat) • Generalized itching of skin especially hands, forehead and eyes in children Note: Skin changes alone without life-threating cardio-respiratory signs do not signify an anaphylactic reaction
Gastrointestinal	• Diarrhoea • Colicky abdominal pain • Vomiting • Incontinence

Time scale	Signs and symptoms of anaphylaxis	Severity
Early warning signs	Dizziness, perineal burning, warmth, pruritus	Mild
	Flushing, urticaria, nasal congestion, sneezing, lacrimation, angioedema	Moderate to severe
	Hoarseness, nausea, vomiting, sub-sternal pressure	Moderate
Late, life-threatening symptons	Bronchospasm, stridor, collapse, hypotension, dysrhythmias	Severe

In general, the more severe the reaction, the more rapid the onset. Most life-threatening reactions begin within 10 minutes of immunization. Keep the recipient under observation for at least 20 minutes after the injection.

Symptoms limited to only one system can occur, leading to delay in diagnosis. Biphasic reactions where symptoms recur 8 to 12 hours after onset of the original attack and prolonged attacks lasting up to 48 hours have been described.

Treatment

Adrenaline (epinephrine): Stimulates the heart and reverses the spasm in the blood vessels and the lung passages and reduces oedema and urticaria, thus countering the anaphylaxis. This very potent agent can however cause irregular heartbeat, heart failure, severe hypertension and tissue necrosis if used in inappropriate doses and routes, though not in anaphylaxis.

Each vaccinator must have an emergency kit with adrenaline, and be familiar with its dosage and administration. The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three or four times a year. Adrenaline that has a brown tinge must be discarded.

Recommended minimum items for an emergency tray	
Evaluation equipment • Sphygmomanometer • Adult and child cuffs • Stethoscope	Drug • Clearly labelled adrenaline (epinephrine) vials • Hydrocortisone vials • Chlorphenamine vials • Oxygen
Treatment equipment • Tourniquet • Disposable syringes • Alcohol swabs • IV solutions (LR, 0.9% Sodium chloride)	Resuscitation equipment • Pocket mask with way valve • Airways (small, medium and large) • Ambu bag • Tongue depressors • ET tubes
Other materials: Laminated copy of updated protocol. Event record sheet/pen/pen torch	

Events happen without warning. Emergency equipment must be immediately at hand whenever immunizations are given. All vaccinators must be familiar with the practical steps necessary to save life following anaphylaxis.

Initial management

- Place the unconscious recipient in the recovery position and ensure the airway is clear.
- Assess breathing and pulse. If the carotid pulse is strong it is not anaphylaxis.
- If appropriate, begin cardiopulmonary resuscitation.
- Give adrenaline (see below for dosage) by deep intramuscular injection.
- If the recipient is conscious after the adrenaline is given, place the head lower than the feet and keep the recipient warm.
- Give oxygen by facemask, if available.
- Send for professional assistance but never leave the recipient alone. Call an ambulance, and medical practitioner if necessary, after the first injection of adrenaline, or sooner if there are sufficient people present.
- If there is no improvement in the recipient's condition within 5 minutes, repeat the dose of adrenaline up to a maximum of three doses. Recovery from an anaphylactic shock is usually rapid after adrenaline.

Note: Hydrocortisone and an anti-histamine may be used as adjunctive medication. Nebulized salbutamol is helpful for bronchospasm and nebulized adrenaline for laryngeal oedema.

Adrenaline in the initial management of acute anaphylaxis			
Drug, site and route of administration	**Frequency of administration**	**Dose (adult)**	**Dose (child)***
Adrenaline (epinephrine) 1:1000 IM to the midpoint of the anterolateral aspect of the middle third of the thigh, immediately	Repeat every 5–15 min as needed until there is resolution of the anaphylaxis. Note: Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity.	0.5 ml.	According to age: <1 year: 0.05 ml. 2–6 years: 0.15 ml. 6–12 years: 0.3 ml. Children > 12 years: 0.5 ml.

*Note: The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into muscle.

This treatment guide is optional and countries may practice their own country specific protocols for treatment of anaphylaxis with drugs of choice and steps to be followed.

Annexure 17

Conducting autopsies in cases of AEFI deaths

Autopsy specimens in an AEFI case resulting in death

It is recommended that in a death suspected to be due to an AEFI, an autopsy 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 could have 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 have 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 vaccinations anywhere else in the world.

2. Objectives of doing an autopsy in AEFI cases

Autopsies done in programme conditions are often for forensic purposes. Hence the usual laid down procedures are followed, without giving importance to the 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 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 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 GoI 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 and 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 i/c 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 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 months 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 due fall from the cot or by parents rolling over the baby)* Anaphylaxis Most often little or no 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 FIR). Medical officer investigating the AEFI should also take a history of the issues discussed in succeeding paras.

3.6.1 Documentation of sleeping environment (if found dead in 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 litres**	
Formalin (formaldehyde soln 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 ($NaH_2PO_4.H_2O$)	4.0	g	20.0	g	200	g
Disodium hydrogen phosphate, anhydrous (Na_2HPO_4)	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 litres	
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 (CH_3COONa)	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 requires 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 ($p < 0.05$) increases of both eosinophil granulocytes (mean 26.6 ± 17.8/SD/) and mast cells (3.2 ± 2.0/SD/) versus controls (eosinophils mean 7.0 ± 10.5 and mast cells mean 0.9 ± 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 between 15mins and 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-third 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. β 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 Postmortem samples

Samples for microbiology, immunology, histopathology and virology should be collected according to the instructions given by the relevant laboratories. Details of instructions on sending samples to specific laboratories can be obtained from the Immunization Division.
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 are obtained from all major organs. Any macroscopically visible lesion 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.
· *Cardiovascular 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 postmortem, 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 the femoral vessels and not from heart blood. Serum should be separated and stored at 40 ^{o}C, 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, 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). The 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 in 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 in 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 in 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 postmortem 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 and 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 and pericardial fluid have limited value as antigen/antibody detection assays cannot be performed using these samples.

Tissue samples, swabs, respiratory secretions are collected in virus transport medium (VTM). VTM can be collected from the Department of Virology, MRI. It can be kept for few weeks at + 40 ^{o}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 the 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.

Form VPD-H002

ACUTE FLACCID PARALYSIS, MEASLES AND AEFI SURVEILLANCE SYSTEM - WEEKLY HOSPITAL REPORT

After review of all wards and registry books, please send this report to the following person every Monday.

Name: _____

Address: _____

Fax: _____

Name of Reporting Hospital:_____ **Year:** [ ]

Week No. [ ] **Period included in the report:** **From:** [ ] **To:** [ ]

Number of cases Identified: **AFP*** [ ] **Suspected Measles**** [ ] **AEFI***** **Serious** [ ] **Severe** [ ]

If no cases were identified, write Zero (0)

Write the case details of AFP cases identified and reported this week

Patient's name and Father's name	Age in months	Sex	Address / Village name and landmark	Block name	District name

Fill up information on all Measles cases below:

Patient's name and Father's name	Age in months	Sex	Received measles vaccine (Y/N/U)#	Village name and landmark	PHC name	Block name	District name	Outcome: Died? (Y/N/U)#

Y=Yes, N=No, U=unknown

Name of person filling this report: _____

Date report sent to District: _____

Approval of Medical Director:_____

*** All cases of AFP in children under 15 years of age should be reported and investigated per guidelines.**
**** All cases of suspected measles of any age should be reported and investigated per guidelines.**
*****All cases of serious/severe AEFI should be reported and investigated per guidelines.**

Form VPD-D001

ACUTE FLACCID PARALYSIS, MEASLES AND AEFI SURVEILLANCE SYSTEM - WEEKLY DISTRICT REPORT

Please send this report to the following person every Tuesday:

Name:_____ Address:_____ Fax:_____

Name of reporting district:_____ Year:

Week No: Period included in the report: From: To:

Number of units expected to report: _____ Number of units reporting on time: _____

Number of cases Identified: **AFP:** | Suspected Measles: | AEFI***: **Serious** | **Severe**

If no cases were identified, write Zero (0)

Names of Reporting Units not reported on time this week:

Write EPID numbers of AFP cases identified and reported this week:

Fill up information on all suspected measles cases below

	Block name	Number of Cases	Number of Deaths	Flagged for preliminary investigation		
				Y / N	If No, give reason	If Yes, allot Outbreak ID (#)
Blocks within the reporting district						
	District total:					

Blocks outside of reporting district

District name	Block name	Number of Cases	Number of Deaths	Cross-notified to the concerned District?		
				Y/N	If No, give reason	If Yes, date cross-notified to the concerned District

Note: The number of measles deaths should be counted as measles cases also.

Cases from previous week should also be considered while flagging for preliminary investigation. Similarly deaths in cases reported from previous weeks should be considered.

The reasons for not flagging for preliminary investigation are:

1 - there are less than 5 suspected measles cases and no deaths in a block in a week

4 - suspected measles cases or death due to measles reported in this week belongs to an already investigated outbreak, In this case mention the outbreak Id. already allotted (#)

Name of person filling out report: _____ Date report sent to State: _____

Approval of District Immunization Officer_____

All districts should report weekly even if no cases of AFP or suspected measles or serious/severe AEFI were identified

Form VPD-S001

ACUTE FLACCID PARALYSIS, MEASLES AND AEFI SURVEILLANCE SYSTEM - WEEKLY STATE REPORT

Please send this report to the following person every Wednesday:

Name:_____ Address:_____ Fax:_____

Name of reporting state:_____ Year:

Week No: Period included in the report: From: To:

Number of units expected to report: _____ Number of units reporting on time: _____

Number of cases Identified: **AFP:** Suspected Measles: AEFI***:

Serious	
Severe	

If no cases were identified, write Zero (0)

Names of Reporting Units not reported on time this week:

Write EPID numbers of AFP cases identified and reported this week:

Fill up information on all suspected measles cases below

	District name	Block name	Number of Cases	Number of Deaths	Flagged for preliminary investigation		
					Y / N	If No, give reason	If Yes, mention Outbreak ID (#)
Blocks within the reporting state							
	State total:						

Districts outside of reporting state:

State name	District name	Block name	Number of Cases	Number of Deaths	Cross-notified to the concerned State?		
					Y/N	If No, give reason	If Yes, date cross-notified to the concerned State

Note: The number of measles deaths should be counted as measles cases also.

Cases from previous week should also be considered while flagging for preliminary investigation. Similarly deaths in cases reported from previous weeks should be considered.

The reasons for not flagging for preliminary investigation are:

1 - there are less than 5 suspected measles cases and no deaths in a block in a week

4 - suspected measles cases or death due to measles reported in this week belongs to an already investigated outbreak, In this case mention the outbreak Id. already allotted (#)

Name of person filling out report: _____ Date report sent to GoI: _____

Approval of State Immunization Officer_____

All states should report weekly even if no cases of AFP or suspected measles or serious/severe AEFI were identified

ACKNOWLEDGEMENT

The revision of the National AEFI Guidelines was commissioned by the Ministry of Health and Family Welfare and its development was carried out under the leadership of Dr Rakesh Kumar, Joint Secretary.

The development of the document was undertaken by a core group established by the Ministry of Health and Family Welfare. Support from Dr Ajay Khera, Deputy Commissioner (CH & I) and Dr Pradeep Haldar, Deputy Commissioner (Immunization) is acknowledged.WHO Country office for India and National AEFI Secretariat at the Immunization Technical Support Unit (ITSU) provided oversight and coordinated the development of the Guidelines. Support from the other vaccine safety stakeholders in the country is deeply appreciated.

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We are sincerely grateful to the members of the National AEFI Committee and other expert reviewers for their painstaking efforts to review and comments on the final draft circulated to them. The reviewers include state and district immunization officials, faculty from medical specialties including pediatrics, epidemiology, community medicine, pathology, pharmacology, forensic medicine and microbiology in medical colleges spread across the country, drug testing laboratories, those working in infectious disease surveillance program and WHO-India field officers.

Notes

World Health Organization
COUNTRY OFFICE FOR India

Developed by WHO Country Office for India on behalf of Ministry of Health and Family Welfare, Govt. of India

Adverse Event Following Immunization Surveillance and Response
OPERATIONAL GUIDELINES, 2015

Ministry of Health and Family Welfare
Government of India