Adverse Events Following Immunization Guideline

2021

Health Protection Agency, Maldives

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) GUIDELINE 2021

VERSION 2

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Contents

Glossary

Adverse event following immunization (AEFI)	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.
Causal association	A cause-and-effect relationship between a causative factor and a disease with no other factors intervening in the process.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
Cluster	Two or more cases of the same event or similar events related in time, geography, and/or the vaccine administered. National programme managers may decide upon a more precise definition. Data mining A field at the intersection of computer science and statistics that attempts to discover inapparent patterns in large data sets.
Immunization anxiety related reaction	An AEFI arising from anxiety about the immunization.
Immunization error related reaction (formerly programmatic error)	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus, by its nature, is preventable.

Immunization safety	The public health practices and policies dealing with the various aspects of the correct administration of vaccines, focusing on minimizing the risk of transmission of disease with the injection and maximizing the effectiveness of the vaccine. The term encompasses the spectrum of events from proper manufacture to correct administration.
Immunization Stress Related Response (ISRR)	Covers an entire spectrum of manifestations to a stress response in the context of immunization/ Immunization anxiety related reaction
Minor AEFI	An event that is not "serious" and that has no potential risk to the health of the recipient of the vaccine.
Signal (safety signal)	Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Surveillance	The continuing, systematic collection of data that is analysed and disseminated to enable decision-making and action to protect the health of populations.
Vaccine	A biological substance that is administered to individuals to elicit immunity (protection) against a specific disease.
Vaccination failure	Vaccination failure is based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Vaccination failure can be due to vaccine failure (either "primary" when immune response is inadequate or "secondary" when the immune response wanes) or failure to vaccinate (i.e. when an indicated vaccine was not administered appropriately for any reason).

Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine product	All components of a given vaccine formulation, including the immunogen (part of the vaccine that stimulates an immune response) and others that may be present such as the adjuvant, preservative and other additives used during the manufacturing process to confirm product quality/stability (e.g. potassium or sodium salts, albumin, gelatin), support growth and purification of specific immunogens (e.g. egg or yeast proteins, antibiotic) or inactivate toxins (e.g. formaldehyde).
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, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
Vaccine quality defect related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.

Abbreviations

ADR Adverse drug reaction

AEFI Adverse event(s) following immunization AFP Acute flaccid paralysis AIDS Acquired immune deficiency syndrome

BCG Bacillus Calmette-Guerin - vaccine for tuberculosis (TB)

DT diphtheria-tetanus vaccine DTP diphtheria-tetanus-pertussis (whole-cell) vaccine

DTP Diphtheria, tetanus and pertussis (vaccine)

EPI Expanded Programme on Immunization

Hib Haemophilus influenzae type b vaccine

HPA Health Protection Agency

MFDA Maldives Food And Drug Agency

MMR Measles-mumps-rubella vaccine

MR Measles-rubella vaccine

NIP National Immunization Program

OPV Oral poliomyelitis vaccine

Td Adult tetanus-diphtheria vaccine

WHO World Health Organization

Introduction:

The National Expanded Program on Immunization (NIP) is considered a success story in Maldives because of its remarkable progress made during the past 25 years. The goal of NIP is to protect the life of thousands of children from premature death and disability from vaccine preventable infectious diseases.

Although modern vaccines are safe but no vaccine is entirely without risk. Some people experience events after immunization ranging from mild side effects to rare serious illnesses. In some cases these reactions are caused by the inherent properties of vaccine; in others, they are caused by an error in transportation, storage, preparation and administration of vaccine; and in majority of cases, there is no relationship.

Adverse event following an immunization may cause concern among the parents and the community and refusal to immunizations for their children may hamper the whole programme. As a result, children are much more likely to get a vaccine-preventable disease, become seriously ill, disabled, and even die. To increase immunization acceptance and improve the quality of services, surveillance of AEFIs must become an integral part of national immunization programme.

NIP is one of the greatest public health successes in Maldives. The accessibility to NIP services is more than 95% since past decade. NIP has prevented children from getting infections against vaccine preventable diseases and saved thousands of children's lives from deaths and continues to prevent deaths each year. As vaccine use increases reports on adverse events following immunization (AEFI) also increases which may have a negative impact on the national immunization programme. An effective AEFI surveillance system, therefore, helps to protect public confidence in the immunization programme.

The purpose of this AEFI surveillance guideline

The guideline is intended to help managers, doctors, nurses and community health workers at central, regional, Atoll and Island levels in AEFI surveillance activities. The guide begins with

- Principles of immunization
- Information on the types of AEFI,
- Detection, reporting, investigation and responding to AEFI
- Data analysis,
- Communication strategy on immunization safety for the parents, health care providers and media and role and responsibilities of each category of health staff involve in the NIP service delivery.

Principles of Immunization

Immunity

Immunity is the ability of the human body to tolerate the presence of material "indigenous" to the human body (self) and to 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 antibody to that organism (antigen, immunogen). Immunity is generally very specific to a single organism or to a group of closely-related organisms. There are two basic mechanisms for acquiring immunity: active and passive.

Active immunity

Active immunity is the stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity for which the protective function of immunization is associated with cells. Usually this lasts for many years, and often for a lifetime. One way to acquire active immunity is to survive infection with the disease causing form of the organism. Upon re-exposure to the same antigen, the memory cells begin to replicate and produce antibody very rapidly to re-establish protection. A safer 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 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) that is

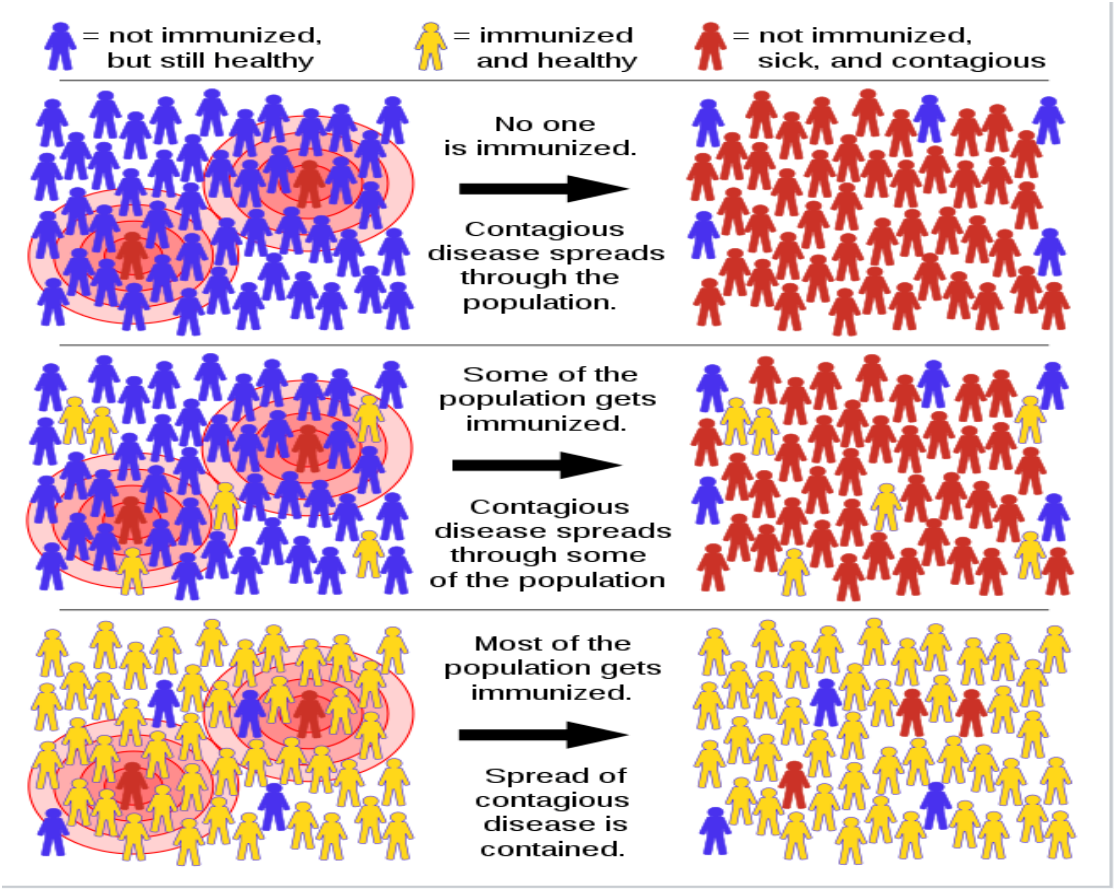
added to improve the immunogenicity of the vaccine. Host factors such as age, nutritional factors, genetics and coexisting disease may also affect the response

Passive immunity

Passive immunity is the transfer of antibody produced by a human or animal to another. This may be natural (from mother to infant) or artificial1 (when high levels of human antibodies specific to a pathogen or toxin are transferred to non-immune individuals) 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. However, maternal antibodies may inhibit successful immunization against live or attenuated live viral vaccines by interfering with vaccine virus growth. For example, vaccination with the live attenuated measles vaccine needs to be given at the appropriate age (usually after 9 months of age) at which time the presence of maternal antibodies (to measles) in the infants has fallen. Passive artificial immunity provides only temporary protection against infection – as short as 1-6 weeks – because the antibodies degrade over time.

Herd immunity

Herd immunity describes immunity that occurs when the vaccination of a portion of the population (the "herd") provides protection to unprotected individuals. Herd immunity theory proposes that, in diseases passed from individual to individual, it is difficult to maintain a chain of infection when large numbers of the population are immune. Hence, the higher the proportion of immune individuals in a population, the lower the likelihood that a susceptible person will come into contact with an infectious agent. Both theoretically and practically, disease usually disappears before immunization levels reach 100%, as has been seen with smallpox and is hoped will happen with 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 and transmissibility of the disease, the efficacy and overall coverage of the vaccine, vaccination coverage among the population at risk and the contact parameter for the population.



The top box shows an outbreak in a community in which a few people are infected (shown in red) and the rest are healthy but unimmunized (shown in blue); the illness spreads freely through the population. The middle box shows a population where a small number have been immunized (shown in yellow); those not immunized become infected while those immunized do not. In the bottom box, a large proportion of the population have been immunized; this prevents the illness from spreading significantly, including to unimmunized people. In the first two examples, most healthy unimmunized people become infected, whereas in the bottom example only one fourth of the healthy unimmunized people become infected.

Figure 1: Herd Immunity

Vaccines

A Vaccine is a biological product that uses body's natural defenses to build resistance to specific infections by inducing formation of protective antibodies, without getting the disease or its complications. A vaccine contains a disease-causing microorganism or virus, or a portion of it, and is often made from either live attenuated or inactivated (killed) forms of the microbe, or from its toxin or one of its surface proteins.

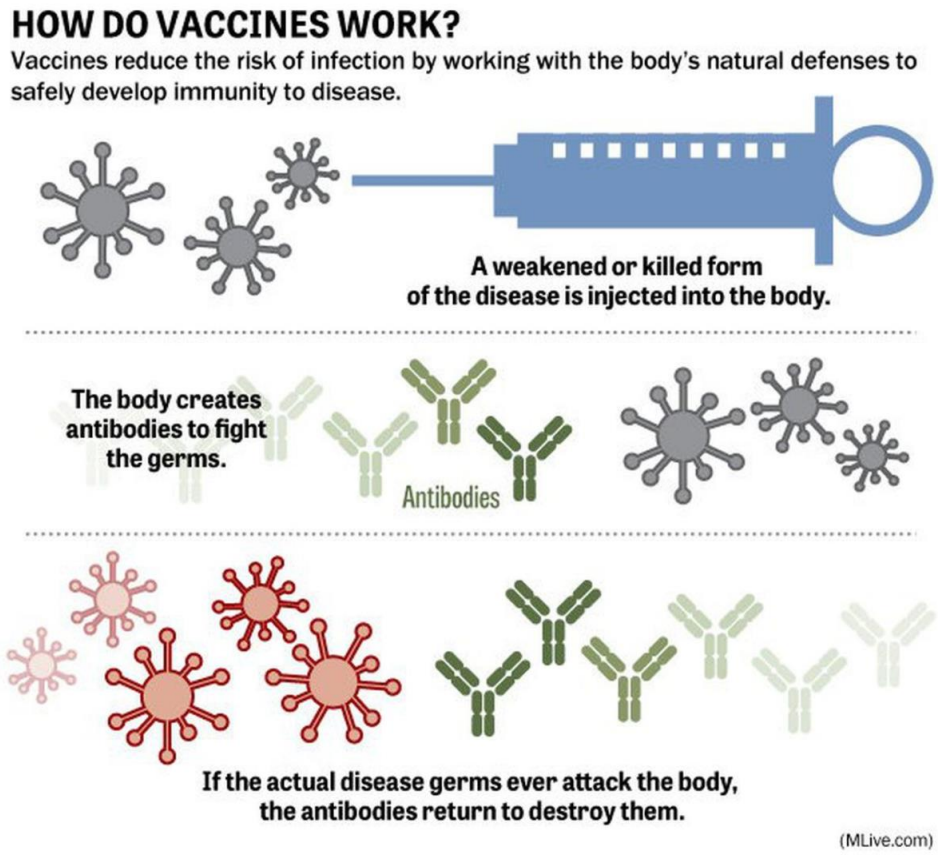


Figure 2: How vaccines work

Vaccines may be monovalent or multivalent (or polyvalent). A monovalent vaccine contains a single strain of a single antigen/immunogen (e.g. measles vaccine), whereas a polyvalent vaccine

contains two or more strains/serotypes of the same antigen/ immunogen (e.g. tOPV and IPV each of which contain three attenuated polio virus types). Combined vaccines contain two or more different antigens (e.g. DTwP, DTPa-HepBHib). The potential advantages of combination vaccines include reducing the cost of storing and administering multiple vaccines simultaneously, reducing the cost of extra health-care visits, improving timeliness of vaccination, and facilitating the addition of new vaccines into immunization programmes. There is no evidence that the administration of several antigens in combined vaccines increases the burden on the immune system, which is capable of responding to millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions and can lead to an overall reduction in adverse reactions. For instance, it can decrease the number of anxiety-related reactions and the chances of immunization error-related reactions.

Table 1:Different Types of Vaccines

Type of vaccines	Example	Details
Live attenuated vaccines	Bacterial: BCG	Use viruses or bacteria that are attenuated, or weakened,. The immune response to a LAV is virtually identical to that produced by a natural infection. Live vaccines are contraindicated in those with immunocompromised state and pregnancy.
	Viral: OPV, MMR, MR, rotavirus vaccine, yellow fever vaccine	
Inactivated (killed antigen) vaccines	Bacterial: Whole cell pertussis vaccine as in DPT	These vaccines are inactivated and can be given even to immunodeficient person. Unlike LAVs, inactivated vaccines are usually not affected by circulating maternal antibodies and do induce an immune response in an infant. They are often more stable than a LAV.
	Inactivated: Inactivated polio virus (IPV)	
Subunit vaccines	Protein based: Hepatitis B vaccine Acellular pertussis vaccine as in DTaP	The whole organism is grown in culture media and then is further processed to purify only those components to be included in the vaccine.
	Polysaccharide: Meningococcal polysaccharide vaccine Pneumococcal polysaccharide vaccine Typhoid Vi polysaccharide vaccine	

	Conjugate vaccine: Haemophilus influenzae type b (Hib) conjugate vaccine, meningitis A and B conjugate vaccine, Pneumococcal conjugate vaccines (PCV-7, PCV-10, PCV-13) Vi conjugate vaccine (Typhoid conjugate vaccine)	
Toxoids	Tetanus toxoid Diphtheria toxoid	While they are no longer toxic, the toxoid is still capable of inducing a specific immune response that is protective against the effect of the toxin.
Nucleic Acid vaccines	COVID-19 vaccines mRNA vaccine (Pfizer vaccine, Moderna vaccine)	Nucleic acid vaccines use genetic material from a disease-causing virus or bacterium (a pathogen) to stimulate an immune response against it. Depending on the vaccine, the genetic material could be DNA or RNA; in both cases it provides the instructions for making a specific protein from the pathogen, which the immune system will recognise as foreign (an antigen).
Viral vector vaccine	COIVID-19 vaccine (Oxford-AstraZeneca Vaccine)	Genetic sequence coding for the antigen from the pathogen into a viral vector that has been previously rendered non-virulent by genetic techniques

Other components of vaccines (excipients)

Adjuvants : Sometimes a substance is added to a vaccine to enhance the immune response by degree and/or duration, thus making it possible to reduce the amount of antigen (immunogen) per dose or the total number of doses needed to achieve immunity. An adjuvant helps slow escape of the antigen from the injection site to lengthen the duration of contact between the antigen and the immune system. The commonlyused adjuvant is aluminium salts (aluminium potassium phosphate or aluminium potassium sulfate) which primarily enhance the immune response to protein. They have been shown to be safe over several decades of use.

Oil-in-water emulsions (ASO3 and ASO4) have used as adjuvants in some vaccines developed in recent years. Rarely, adjuvants may cause injection site reactions – including subcutaneous nodules, sterile abscess, granulomatous inflammation and contact hypersensitivity – particularly if the administration

technique is wrong (e.g. subcutaneous). Adjuvant-containing vaccines should be administered intramuscularly.

Antibiotics: are used during the manufacturing phase 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 micrograms 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 at once. Neomycin allergy is very rare.

Preservatives: These are chemicals (e.g. thiomersal, phenol derivatives) that are added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and prevent serious secondary infections in multidose vials as a result of bacterial or fungal contamination. Thiomersal, which contains ethyl-mercury, has been subject to intense public scrutiny but there is no evidence of any toxicity from thiomersal in vaccines (Formaldehyde, an inactivating agent, is used during the manufacturing process to inactivate viruses and bacteria and detoxify toxins and is removed almost completely during the purification process.) Stabilizers Stabilizers are used to help the vaccine maintain its effectiveness during storage. To confirm product quality (antigenicity) or stability, compounds may be added to vaccines to address problems with acidity, alkalinity (pH), stability and temperature. Vaccine stability is essential, particularly if the cold chain is unreliable. Instability can cause decreased infectivity of LAVs and loss of vaccine antigenicity. Bacterial vaccines

Contraindications and precautions

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and be uptodate on the product details and vaccinators should check the specific product information about the vaccines they are administering (should be familiar with the information on the product insert) This includes information on vaccine handling, side effects, contraindications and precautions etc, this is especially important if giving new vaccines or optional vaccines.

As with all vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine. The administration of vaccines should be postponed in subjects suffering from moderate to severe illness with or without fever. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

A contraindication to vaccination is a rare characteristic in a recipient that increases the risk of a serious adverse reaction. Ignoring contraindications can lead to avoidable vaccine reactions. One of the most serious reactions following vaccination is anaphylaxis which is the only contraindication applicable to

subsequent doses of the same vaccine. Most contraindications such as severe acute illnesses (e.g. acute respiratory tract infection) or treatment with steroids are temporary and the vaccination can be administered later. These are called temporary or relative contraindications.

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

Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

Table 2: Contraindication and Precautions to vaccination

Vaccine	Contraindication	Precaution
DT, dT	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid—containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine Moderate or severe acute illness with or without fever Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid—containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10

		years have elapsed since the last tetanus-toxoid-containing vaccine Moderate or severe acute illness with or without fever
DPT DTaP Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP or Tdap	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized GBS <6 weeks after previous dose of tetanus-toxoid–containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever
HepB	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Hypersensitivity to yeast	Moderate or severe acute illness with or without fever
HiB	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age <6 weeks	Moderate or severe acute illness with or without fever
HPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component, including yeast	Moderate or severe acute illness with or without fever
IIV (inactivated influenza vaccine)	Severe allergic reaction (e.g., anaphylaxis) after previous dose of influenza vaccine or to vaccine component.	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever Egg allergy other than hives, e.g., angioedema, respiratory distress, light headedness, recurrent emesis; or required adrenalin or another

		emergency medical intervention (IIV may be administered in an inpatient or outpatient medical setting and under the supervision of a health care provider who is able to recognize and manage severe allergic conditions).
IPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
MMR	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy[(h)] or patients with HIV infection who are severely immunocompromised) Congenital or hereditary immunodeficiency in first-degree relatives (unless immunocompetence of recipient has been verified)	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) History of thrombocytopenia or thrombocytopenic purpura. Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing as MMR vaccination reduces reactivity of the tests with (can give on the same day as vaccination or wait for ≥4 weeks after TST). Moderate or severe acute illness with or without fever
PCV (pneumococcal conjugate vaccine)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose of PCV13 or any diphtheria-toxoid–containing vaccine or to a component of a vaccine (PCV13 or any diphtheria-toxoid–containing vaccine), including yeast	Moderate or severe acute illness with or without fever
PPSV23	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
Rotavirus	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component SCID History of intussusception	Altered immunocompetence other than SCID Chronic gastrointestinal disease[(k)] Spina bifida or bladder exstrophy[(k)] Moderate or severe acute illness with or without fever

Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap	GBS <6 weeks after a previous dose of tetanus-toxoid–containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid—containing or tetanus-toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever
Varicella	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, long-term immunosuppressive therapy or patients with HIV infection who are severely immunocompromised) PregnancyCongenital or hereditary immunodeficiency in first-degree relatives (unless immunocompetence of recipient has been verified)	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) Moderate or severe acute illness with or without fever Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination) Use of aspirin or aspirin-containing products
COVID-19 vaccine (ChAdOx1 S [recombinant]) (Astrazeneca/ Covisheild vaccine)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with COVID-19 Vaccine AstraZeneca/Covishield vaccine	Administration of the COVID-19 Vaccine AstraZeneca in patients with a history of heparin-induced Thrombocytopenia and thrombosis (HITT or HIT type 2) or cerebral venous sinus thrombosis, history of idiopathic splanchnic (mesenteric, portal, splenic) venous thrombosis, history of anti-phospholipid syndrome (APLS) with thrombosis. Anaphylaxis to other vaccines or to other medicines.

Pfizer vaccination	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Myocarditis and/or pericarditis attributed to a previous dose	Anaphylaxis to other vaccines or to other medicines. Following conditions, evaluation by clinician or by immunisation program about the best timing of vaccination is recommended: Recent (i.e., within the past 6 months) inflammatory cardiac illness e.g., myocarditis, pericarditis, endocarditis, Acute rheumatic fever (i.e., with active myocardial inflammation) or acute rheumatic heart disease, People aged 12-29 years with dilated cardiomyopathy, Complex or severe congenital heart disease including single ventricle (Fontan) circulation, Decompensated heart failure, Cardiac transplant recipients.

Notes:

- For the purpose of this guidance, an immediate allergic reaction is defined as any hypersensitivity-related signs or symptoms, such as urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within 4 hours following exposure to a vaccine or medication.
- Live injectable vaccines (such as MMR and varicella-containing vaccines) can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days
- A substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html

https://www.health.gov.au/sites/default/files/documents/2021/08/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021.pdf

AEFI Surveillance

A. General definition:

Adverse event following immunization1 (AEFI): any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease

Adverse event of special interest (AESI): A relatively new AEFI classification that started with pandemic vaccine development. AESI refers to adverse events of significant scientific, medical and public interest among pandemic vaccine.

Goals:

The goal of AEFI surveillance is to:

1. Find the cause of an AEFI or cluster of AEFIs and correct it
2. To monitor the quality and safety of vaccine and enforce good immunization practices
3. Assure the public of the integrity of the immunization services and increase public confidence in immunization

Objectives:

The objective of AEFI surveillance is to:

1. To detect and manage serious AEFI cases
2. To report AEFI using standard case definition
3. To take appropriate regulatory actions when serious and unexpected AEFIs detected
4. Identify unusual high rates of AEFI with specific vaccine lots and brands
5. Promptly address programmatic errors through implementation of corrective measures
6. Ensure that coincidental events are not falsely blamed on immunization
7. Maintain confidence in the immunization programme by properly responding to concerns
8. Estimates AEFI rates in the population compared with local and global data

B. Types of immunization safety surveillance (global AEFI surveillance)

Passive surveillance: This encompasses all spontaneous AEFI reporting from immunization service providers/hospitals/patients to the first administrative level (e.g. divisional, municipality, township) in the surveillance system. From there, reports are sent to the next reporting subnational level(s), ending at the national-level unit and global institutions responsible for AEFI surveillance. Passive surveillance systems theoretically allow anyone in a country to report, and due to their broad coverage they can provide the first indication of an unexpected AEFI. Therefore, the main strength of passive surveillance is to detect early the unknown serious AEFI (signals). However, passive surveillance has many limitations, including underreporting. Thus, passive surveillance is often not useful for determining whether the rate of an adverse event has increased. Thus, newly introduced vaccines and/or special immunization campaigns should have

added layers of active surveillance and/or epidemiological studies to maximize the effectiveness of passive AEFI surveillance (e.g. enhanced spontaneous surveillance introduced during special immunization campaigns to encourage reporting by service providers or receivers).

Active surveillance: This is primarily used for characterization of the AEFI profile, rates and risk factors, but logistical and resource constraints limit its wide application. Countries may carry out active AEFI surveillance only for selected AEFI at selected institutions (sentinel sites). Active surveillance can also be carried out in the community setting (e.g. cohort event monitoring).

In this manual, the focus is on routine Immunization safety i.e. passive surveillance systems at subnational, national and international levels to ensure effective monitoring and prompt action in response to AEFI. However, within or parallel to the spontaneous reporting of a passive system, an active surveillance system can be established with specific objectives for a specified time period. Immunization safety surveillance needs to be a collaborative venture between the immunization programme and, when it exists, the NRA, as both parties are responsible for the safety of vaccines. Depending on the country's administrative and operational structure, one unit/institution needs to be the focal point for immunization safety surveillance. As the unit's independence is important, the task can be delegated to another organization or pharmacovigilance centre (e.g. a university department) as long as the links with the NRA and the national immunization programme are maintained. It is important to note that maintaining high levels of transparency and independence are key factors which are necessary for building and maintaining public trust in the AEFI surveillance system. Immunization safety reporting systems should build on and mutually strengthen any existing system of reporting information (e.g. immunization coverage reports,

disease incidence reports, and adverse drug reaction reports). The best AEFI reporting system is the one which encourages a high level of appropriate reporting and takes timely action in response to reports.

Key elements of an effective AEFI surveillance system include:

1. Commitment of health policy makers, health manager and health workers
2. AEFI surveillance is integrated within the Adverse Drugs Reaction surveillance system
3. Establish national AEFI committee to analyze AEFI data and conduct causality assessment and regular meeting to address vaccine safety concerns
4. Develop guideline including case definitions and clear descriptions of reporting and focal person at each level.
5. Ensure trained health workers including managers and supervisors
6. Establish Communication plan to inform public about AEFI and address risks of lost of public confidence in the immunization

C. Cause-specific definitions or AEFI

AEFI are classified into 5 types based on the cause specific reactions. These are described below:

Table 3: AEFI classification: Cause Specific reactions

Type of AEFI	Definition
Vaccine product-related reaction	AEFI that is caused or precipitated by a vaccine due to one more inherent properties of the vaccine
Vaccine quality defect-related reaction	An AEFI that caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Immunization error-related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration
Immunization anxiety related reactions or Immunization stress related response (ISRR)	An AEFI arising from anxiety about the immunization process. ISRR: cover the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety.
Coincidental Event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

Vaccine product-related reaction

Vaccine product-related reaction, is an individual's reaction to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. Most often the exact mechanism of a vaccine product-related reaction is poorly understood. The reaction may be due to an idiosyncratic immune mediate reaction (e.g. anaphylaxis) or to replication of the vaccine-associated microbial agent (e.g. vaccine-associated poliomyelitis following OPV which contains attenuated live virus). However, it is important to note that, these rare vaccine product-related reactions which do not occur in the majority of vaccines recipients.

Vaccine quality defect-related reactions:

An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer. Quality defect is defined as any deviation of the vaccine product as manufactured from its set quality specifications. With introduction of Good Manufacturing Practices (GMP), the vaccine manufacturers have started following GMP. Together with establishment of GMP the strengthening of National Regulatory Authorities (NRAs) have resulted in the potential risk of such quality defects being very rare now.

Example: *Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine Inactivated polio vaccine (IPV)An inactivated (killed) polio vaccine. Unlike oral polio vaccine (OPV), a LAV vaccine, IPV must be injected to produce the desired immune response.*

Immunization error- related reaction

The immunization error related reaction are classified into three major categories based on their preventable nature, the mechanisms focus on the nature of the error rather than on the biological process (es) giving rise to the specific AEFI(s).

1. Error in vaccine and diluent handling

2. Error in vaccine prescribing or non-adherence to recommendations for use
3. Error in administration

Immunization error- related reactions are the most commonly reported adverse events. These occur as a result of inappropriate storage, transportation, reconstitution, preparation and administration of vaccines. It is extremely important that these AEFIs are reported and addressed for early correction. Table-3 provides three major types of Immunization error and related reactions:

Immunization error- related reactions may also 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.

Table 4: Immunization Error Related AEFIs

Immunization Errors	Adverse Events/reactions

1. Error in vaccine handling: a) exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine and diluents b) Use of vaccine after expiry date	a) i) Vaccine ineffective as a result of inactivation of vaccine components ii) Systemic or local reaction due to changes in the physical nature of the vaccine e.g. in injection site abscess, cellulitis, sepsis, toxic shock syndrome etc b) Vaccine ineffective
2. Error in vaccine prescribing or non-adherence to recommendations: **a) Failure to adhere to a contraindication:** Pentavalent vaccine given ignoring convulsion history with previous dose;	a) Anaphylaxis after vaccination to an individual known to have hypersensitivity b) Disseminated infection with attenuated live vaccine agent after administration to an individual with known immunodeficiency and contraindicated for any live vaccine.
b. Failure to adhere to vaccine indications: dose, route/site: i) Incorrect dose ii) Incorrect age group iii) Incorrect injection site, equipment or injection technique (Subcutaneous instead of intra-dermal BCG or IM instead of subcutaneous, too superficial toxoid vaccination (DPT, DT, TT, Pentavalent vaccine), administration in the buttocks.	• Local and or systemic reaction • Vaccine failure • Neurological, muscular, vascular or bony injury, • Sciatic nerve damage
3. Error in administration: a) Use of incorrect diluent or incorrect vaccine other than the intended vaccine/diluent b) Incorrect sterile technique or inappropriate procedure with a multi-dose vial • contaminated vaccine or diluents • reconstituted vaccine after 6 hours or at subsequent session c) Failure to ensure a safe environment during and immediately following immunization d) Inadvertent administration of vaccine to someone for whom it was not intended	a.i) Failure to vaccinate ii) Reaction due to inherent properties of whatever was administered other than the intended vaccine/diluent b. i) Infection at the site of injection due to a microbial contaminant introduced during administration of the vaccine b.ii) Infection beyond the site of injection due to a microbial contaminant introduced during administration of the vaccine. c.i) Head injury during a syncopal episode post-immunization d.i) e.g. via a needle stick injury or splash to the eye

Immunization anxiety-related reaction/ Immunization Stress Related Response

The types of reactions caused by immunization anxiety include but are not limited to:

- Vasovagal mediated reactions

- Hyperventilation mediated reactions
- Stress-related psychiatric disorders

Immunization Related Stress Response (ISRR)cover the entire spectrum of manifestations (symptoms and signs) of a stress response rather than a single symptom, anxiety. Stress response that occurs around the time of immunization is influenced by physiological, psychological and social factors.

Table 5: Factors Influencing Stress Response to Immunization

BIOPSYCHOSOCIAL FACTOR	PRE-EXISTING CONDITIONS (HISTORICAL)	CONDITIONS OCCURRING DURING IMMUNIZATION (DYNAMIC)
Physiological	• **Age:** adolescence is a period of risk for vasovagal reactions. • **Sex:** females are more predisposed to vasovagal reactions. • **Weight:** lower body mass index increases the risk of vasovagal reactions[4]	• Physiological stress response to pain, such as change in heart rate or blood pressure: acute stress response
Psychological	• Temperament (personality) • Ability to understand and reason, which depends on developmental age and cognitive understanding • Preparedness: prior knowledge of immunization by injection • Underlying anxiety • Previous experience	• Underlying psychological factors (e.g. anxiety and fear) that may affect the perception of symptoms after an injected vaccine, such as pain at the injection site, dizziness due to a vasovagal reaction or fever and lethargy as part of the expected immune response to the vaccine
Social	• Community trust in health care • Community perceptions, norms and values about immunization • Community and family support for immunization • False or misleading news reports and social media messages about immunization • Experience of peers	• Behaviour of health care workers and observers (e.g. family, friends) • Behaviour of others being vaccinated (e.g. during mass or school campaigns)

Coincidental event

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

1. Underlying or emerging condition(s) in the vaccine

a) Manifestation or complication of a congenital or inherited underlying disease condition or birth injury.

b) Manifestation or complication of an underlying acquired disease condition that may or may not have been diagnosed prior to immunization.

c) Psychogenic illness.

d) Conditions caused by exposure to something other than vaccine:

e) Infection due to agents such as bacteria, viruses, fungi or parasites.

f) Adverse reaction due to recent or concomitant medication or use of illicit substances.

g) Allergic and other hypersensitivity reactions due to exposure to allergens other than those present in the vaccine.

h) Injury due to exposure to environmental toxins.

i) Injury due to trauma including surgery

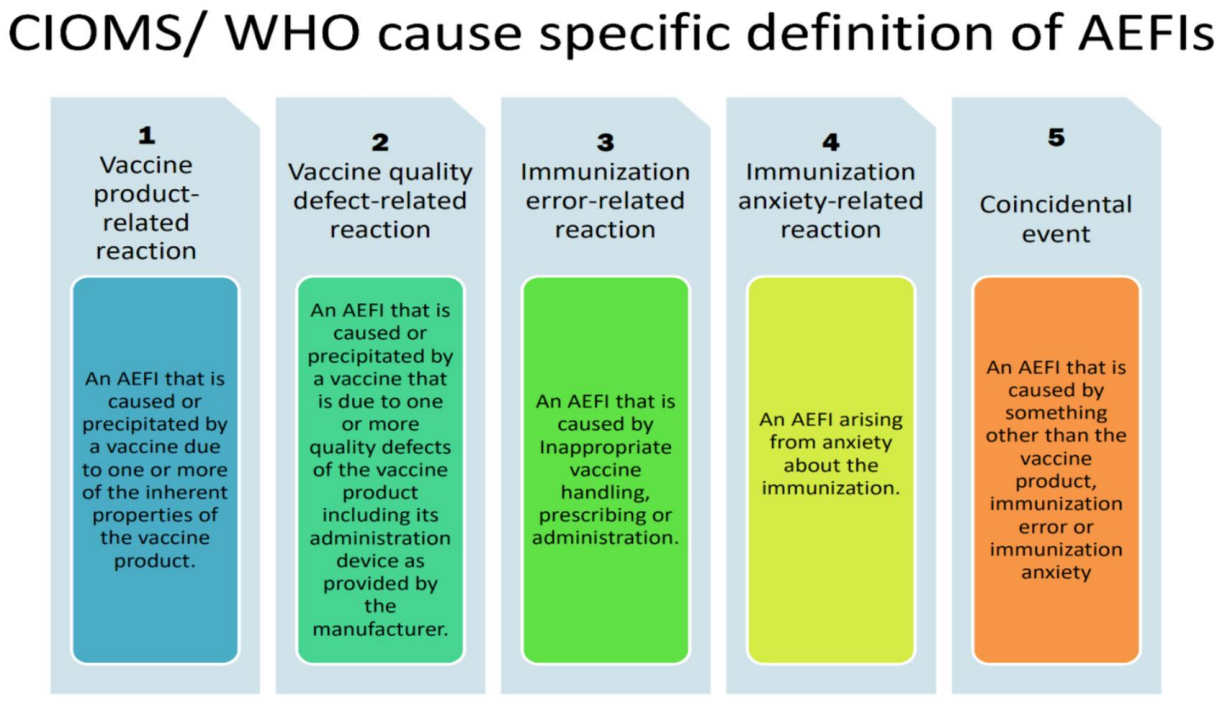


Figure 3: Cause Specific AEFIs

Vaccine Reactions by Seriousness and Frequency

Most vaccine reactions are minor and subsides on their own. Serious reactions are very rare and, in general do not result in death or long-term disability

Table 6: Frequency of Occurrence of Reported Adverse Events

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

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 antigens. Local site reaction, fever and systemic symptoms can result as part of the immune response. In addition, some of the vaccine's components (e.g. adjuvant, stabilizers or preservatives) can lead to reactions. An effective and safe vaccine produces the best possible immunity and reduces these reactions to a minimum. The occurrence of local reactions such as pain, swelling and/or redness at the injection site varies by the type of antigen. For example, these local reactions are reported very commonly (>10%) with whole-cell DTP, whereas for acellular DTP it is only a common reaction with a frequency of 1-10%. BCG causes a specific local reaction which starts as a papule (lump) two or more weeks after immunization, then becomes ulcerated and heals after several months, leaving a scar. Keloid (thickened scar tissue) from the BCG lesion is more common among African and Asian populations. The occurrence of systemic reactions also varies by the type of antigen. Fever is a very common (>10%) systemic reaction reported for most antigens. Other common systemic reactions (e.g. irritability, malaise, loss of appetite) can also occur after many antigens, and DTwP has more reports of these systemic reactions than DTaP. For LAVs such as measles/ MMR and OPV, the systemic reactions can occur from vaccine virus infection. Measles vaccine can cause fever, rash and/or conjunctivitis but this is very mild compared to "wild" measles. However, it can be serious, and even fatal, for severely immunocompromised individuals. Vaccine reactions for mumps vaccine (parotitis, swollen parotid gland) and rubella vaccine (joint pains and

swollen lymph nodes) are uncommon and affect less than 1% of children. Rubella vaccine commonly causes symptoms in adults, with 15% suffering from joint pains. Systemic reactions from OPV are uncommon and affect less than 1% of vaccines with diarrhea, headache and/or muscle pain.

Mild fever, irritability, malaise and loss of appetite frequently occur with certain vaccines, which are usually self-limiting. However, such symptoms are usually mild, but can be quite serious in severely immune-compromised children.

It is important to note that these vaccine reaction rates are an expected response to the vaccine antigen. However, if the observed vaccine reaction rate is significantly higher than the expected vaccine reaction rate for any vaccine, an investigation is needed to explain this.

Table 7: Summary of Common and mild adverse events following immunization

Vaccine	Local reaction (pain, swelling, redness)	Fever	Irritability, malaise and non-specific symptoms
BCG	Common	Rare	Rare
Hepatitis B	Children up to 5%	1-6%	Rare
Hib Pentavalent	5% - 15%	2-10%	Rare
Measles	~10%	5-15%	5% rash
OPV	None	Less than 1%	Less than 1% [1]
TT	~10% [2]	~10%	~ 25%
DPT [3]	Up to 50%	Up to 50%	Up to 60%
Management	- Paracetamol [4]	- Give extra fluids - Wear cool clothing - Tepifd sponge or bath - Paracetamol	Symptomatic

[1] Diarrhea, Headache, and/or muscle pains
[2] Rate of local reactions likely to increase with subsequent doses, up to 50 to 85%
[3] with whole cell Pertussis vaccine; A cellular Pertussis vaccines rate are lower.

4 Paracetamol doses: up to 15 mg/kg every 4 hours, maximum of 4 doses in 24 hours

Serious AEFIs

An AEFI will be considered serious if it results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, clusters, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above should also be considered serious after applying medical and scientific judgment. To increase immunization acceptance and improve the quality of services, the surveillance of severe AEFIs must become an integral part of immunization programme.

It is important to note that 'serious' and 'severe' are often used as interchangeable terms but they are not. 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.

These may occur in rare cases. Some of these do not lead to long-term effects (e.g. seizures, hypotonic hypo responsive episodes). Anaphylaxis, while potentially fatal, is treatable without leaving any long-term effects.

However, there are few reactions with long-term consequences (e.g. VAPP, BCG Osteomyelitis etc.).

All serious vaccine reactions need to be reported as AEFI and require investigation.

Table 8: Summary of Rare Serious Adverse Events, Onset Interval and Rate by Antigen

Vaccine	Reaction	Onset interval	Number of events per million doses
BCG	- Suppurative lymphadenitis	2-6 months	100-1,000
	- BCG osteitis/ osteomyelitis	1-12 months	1-700

	- Disseminated BCG infection	1-12 months	2
Hepatitis-B	- Anaphylaxis	0-12 hour	1-2
Hib	- Nil / not known		
Measles [1]	- Febrile seizures	5-12 days	333
	- Thrombocytopenia (low platelets)	15-35 days	33
	- Anaphylaxis	0-12 hour	~1
OPV	- Vaccine associated paralytic poliomyelitis (VAPP)	4-30 days	0.76-1.3 (1st dose) 0.17 subsequent doses
TT	- Brachial neuritis	2-28 days	5-10
	- Anaphylaxis	0-12 hour	1-6
	- Sterile abscess	1-6 weeks	6-10
DPT	- Persistent (>3hours) inconsolable screaming	0-24 hours	1,000-60,000
	- Seizures [2]	0-3 days	570
	- Hypotonic hypo responsive NIPsode (HHE)	0-24 hours	570
	- Anaphylaxis	0-12 hour	20
	- Encephalopathy	0-3 days	0-1

1 Approximately 85% of those receiving a second dose are already immune. Reactions do not occur if the child/woman is already immune. This is not the case for anaphylaxis, where this type of reaction is more likely on the second or subsequent doses.

2 Seizures are most likely febrile in origin, and rate depends on past history, family history and age, with much lower risk in children under the age of 4 months

The time interval to onset will depend on the antigen and the adverse reaction. For detailed information on antigen or adverse reaction-specific onset intervals, refer to the Brighton Collaboration case definitions (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html),

Detecting and Reporting AEFI

Case detection is the first important step in AEFI surveillance. The primary reporter (i.e. the one who first reports an AEFI) may be a field health worker, clinic or hospital staff, a volunteer, parent or any other person who detects the AEFI.

Detection of any serious events after vaccination and suspicion alone is sufficient for reporting. Rapid detection and evaluation of a possible link to vaccines is essential to ensure the continued safety of vaccines. Thus, in case of a suspected AEFI, it is preferable to submit a report (via online mechanism or by filling the AEFI reporting form available in all health care facilities) rather than waiting for all aspects of an investigation to be completed. This is particularly true for serious AEFIs. All of the following adverse events should be reported if temporally related to immunization. Unless otherwise specified this includes all such events occurring within 30 days of a vaccine administration.

For newly rolled out vaccines such as CVOD-19 vaccines even minor AEFis such as fever and local reactions should be reported if the care giver notifies to the health care provider.

AEFI requiring reporting

1. All serious AEFIS
    a. Death attributed to vaccine
    b. Life threatening event
    c. AEFI that resulted in hospitalization or prolongation of existing hospitalization
    d. AEFI resulting in persistent or significant disability or incapacity.
    e. Congenital anomaly or birth defect
2. Clusters of AEFI
3. Part of a suspected signal
4. AEFi caused by suspected immunization error
5. Any AEFI causing significant parental or community concerns
6. Other AEFI as given below should also be reported
    a. Local reactions being notified to the health care provider (may signal immunization error),
    b. Acute flaccid paralysis
    c. Hypotonic hyporesponsive episodes
    d. Brachial nueritis
    e. Lymphadenopathy/ lympahdenitis

f. Persistent inconsolable screaming
g. Thrombocytopenia
h. Toxic Shock Syndrome

Table 9: List of reportable AEFI

Reportable AEFI	Time of onset following immunization*
• Acute flaccid paralysis for OPV recipient • Acute flaccid paralysis for contact of OPV recipient	• 4-30 days following immunization • 4-75 days following immunization
• Anaphylaxis (after any vaccine)	• Within 48 hours of immunization
• Brachial neuritis	• 2-28 days following immunization
• Disseminated BCG infection after BCG vaccine	• Between 1 and 12 months
• Encephalopathy	• 0-12 days following immunization
Hypotonic hyporesponsive episode (HHE) after DTP/PVV vaccine	Median time is 3-4 hours after immunization, but ranges from immediate to 48 hours. However, it can occur even after 48 hours
Injection site abscess (bacterial/sterile) after any injectable vaccine	Not specific. However, commonly within first 14 days of immunization
Intussusception (after rotavirus vaccines)	Commonly within 21 days, risk increased after the first 7 days and usually first dose
• Lymphadenitis after BCG vaccine • Osteitis/osteomyelitis after BCG vaccine	Between 1 and 12 months
Persistent (more than 3 hours) inconsolable screaming after DTP/PVV vaccine	Common immediately and up to 48 hours of immunization. However, it can occur even after 48 hours
Sepsis (after any injectable vaccine)	Within 7 days following immunization
Seizures, including febrile seizures • after measles/MMR	• 6-12 days following immunization

• after DTP/PVV	• 0-2 days following immunization
Severe local reaction (after any injectable vaccine)	Within 7 days following immunization
Thrombocytopaenia (after measles/MMR)	Median time is 12-25 days after immunization, but the range is 1-83 days
Toxic shock syndrome (TSS) (after any injectable vaccine)	Commonly within 72 hours following immunization
GBS	1-42 days
Myocarditis / pericarditis	1-42 days
Myelitis	1-42 days
Thrombotic Thrombocytopenic Syndrome-TTS (COVID-19 viral vector vaccine)	1-30 days
Death Hospitalization Disability Any other severe and unusual events that are attributed to immunization by health workers or the public	No time limit, but in general those within 30 days following any immunization. For newly introduced vaccines longer reporting times from 3 months to one year maybe employed.
*The time interval to onset will depend on the antigen and the adverse reaction. For detailed information on antigen or adverse reaction-specific onset intervals, refer to the Brighton Collaboration case definitions (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html), WHO position papers and observed rates information sheets (http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/index.html, accessed 1 August 2014).	

If the AEFI does not occur within the time frame specified, but there is a suspicion that the event may be related to vaccine, then these should also be reported. If the adverse event occurs outside of this time frame, the event is less likely to be due to vaccination.

Program Implementation Level, Responsibility and Surveillance activities

AEFI reporting from Health Facility

Health care providers of Health Facilities detecting AEFI should report all serious, clusters AEFIs to CSFP immediately and CSFP should in turn inform the even to NIP immediately. The AEFI reporting form should be submitted within 24 hours of detecting any serious or AEFI of public concern, or cluster. Non serious AEFI maybe reported within 7 days of detection.

The CSFP (Medical Officer/Nurse) with assistance from PHU will report all AEFIs including zero reporting of the Island to Programme manager using AEFI monthly compilation form (Appendix-4). The report should reach to Programme Manager by 1st week of following month. Clinical Surveillance focal point (CSFP) with assistance from PHU will be preparing the monthly AEFI line list (appendix-4.A).

The Public Health Unit (immunization focal point) will submit all AEFIs reported in each month in AEFI monthly compilation form (Appendix-4) to Health Protection Agency (HPA), NIP unit. Clinical Surveillance will help PHU in compiling the reports. The report should reach HPA, NIP Unit by 15th of the following month.

Serious AEFIs should be reported immediately:

Death and hospitalization should receive immediate attention and should be reported to Clinical Surveillance Focal Point as soon as they are detected. Cluster of events (abscesses and lymphadenitis) should be reported immediately while other AEFIs should also be uploaded in to the system within 24hours. Once Medical Officer/Consultant is notified of the above events she/he will immediately notify to HPA, NIP Manager and will initiate an investigation. If these events occur in a Hospital/Health Facility respective CSFP will immediately notify to NIP Manager who will initiate an investigation based on decisions made by the AEFI committee.

All AEFIs, including those reported (via phone or online form filling) immediately during the month, should be counted in routine, written, monthly surveillance report. During monthly AEFI line listing if any cluster is identified Medical Officer will initiate investigation and take necessary actions to prevent further occurrence of similar event.

Role and Responsibilities:

Community Health Workers/Nurse

- Identify and report AEFI timely
- Refer AEFI case to health Facilities/hospital
- Reassure the parents/community
- Correct programme error

Medical Officer in Hospital

- Identify AEFI
- Report to Clinical Surveillance Focal point or Public Health Unit within 24 hours
- Assist with diagnosis of AEFI
- Ensure appropriate case management
- Cooperate with the Investigation Team
- Inform AEFI committee and Programme immediately of deaths and hospitalization

National Immunization Programme / HPA

- Ensure a functioning national AEFI surveillance system in the country
- Encourage reporting of AEFI
- Collate all AEFI reports nationally, maintain a database and regular feed back
- Ensure adequate supply of AEFI forms and other logistics at all level
- Initiate investigation if clusters are detected at national level or any AEFI with NIP concern
- Provide support to conduct proper investigation at atoll/Island level
- Communicate findings of investigation of serious AEFIs with all stake holders including media
- Support activities of NCIP
- Facilitate implementation of the recommendations of NCIP
- Assure public awareness on immunization safety
- Communicate and collaborate with MFDA, NHL and partner agencies (WHO, UNICEF)
- Respond to crisis
- Monitoring and Evaluation of AEFI Surveillance System

NIP Unit will compile and analyze AEFI reports on monthly basis and provide one copy to Maldives Food and Drug Authority (MFDA), National Health Laboratory (NHL). In case of death, hospitalization, cluster or significant parental/community concern, NIP Unit will communicate with local health authority and assist in responding to the AEFI. NIP may seek assistance from the national AEFI committee whenever needed. NIP unit will coordinate with national AEFI committee to investigate serious AEFIs. It is the responsibility of NIP to provide feedback to the Atolls, Islands Hospital and health authorities regularly. This may be done through regular NIP bulletin, official letter, review meetings and verbal communications.

Maldives Food and Drug Authority (MFDA)

- Ensure participation of a member in NCIP
- Inform NIP Unit of any AEFI reported directly to FDA via the Adverse Drug
- Reaction Reporting System
- Implement any regulatory action if necessary
- Participate in investigation of serious AEFI
- Implement recommendation by the NCIP

National Health Laboratory (NHL)

- Ensure participation of a member in NCIP
- Inform NIP Unit of any AEFI reported directly to NHL
- Provide or facilitate Quality/Safety testing of Vaccines in AEFI investigations
- Implement recommendation by the NCIP

National AEFI Committee

- NIP epidemiologist / Public Health Specialist
- Pediatrician
- Infectious Disease Specialist
- Emergency Physician
- Adult Physician
- Nurse
- Representatives from Maldives Food and Drug Authority and Quality Assurance and Regulatory Division (QARD), MOH can be on the panel as ex-officio members and may be invited, when required
- Representative from partner agencies such as WHO and UNICEF can be on the panel as ex-officio members and may be invited, when required
- Regional / Atoll Focal Points, can be on the panel as ex-officio members and may be invited, when required

Clinical Surveillance focal point (CSFP)

Clinical Surveillance focal point can be a Medical Officer/Nurse of Health Facilities for Islands.

Investigation of all serious AEFI will be conducted under guidance of NIP and AEFI committee.

Serious AEFI should be reported immediately to the NIP by phone. Othe reportable AEFIs should be reported within 24 hours of AEFI reporting. The clinical surveillance focal point (CSFP), a doctor or nurse involved in patient care, of Islands and Atolls should monitor the number of cases of each trigger event that have been reported by each health center/hospital each month. In this way, CSFP can identify patterns, such as clusters, within or across health centers/hospitals and take appropriate action. The CSFP should work together with the Public Health Unit (PHU).

Role of clinical surveillance focal point

- Ensure a functioning AEFI surveillance system in the Island and Atoll
- Compile all reports of AEFI and timely submit to HPA, NIP
- Notify serious AEFIs to NIP
- Monitor timely reporting of AEFI
- Initiate and facilitate investigation of serious AEFI
- Ensure appropriate case management
- Ensure enforcement of corrective action
- Analysis of AEFI data and feed back to Health facilities
- AEFI Surveillance review with Medical officer/Nurse
  Communicate with and handle the media appropriately if needed, under guidance of NIP/HPA

Public Health Unit (PHU)

Public Health Unit will also assist CSFP in carrying out his/her responsibilities in AEFI reporting and investigation.

Role of PHU

- Ensure appropriate case reporting and management of an AEFI
- Encourage Health workers/vaccinators to report AEFI
- Assist CSFP to analyze AEFI data with guidance from NIP unit or Surveillance unit of HPA and maintain monthly line list and timely monthly report to Director/Manager of Hospital and NIP unit
- Provide feedback to community health workers and nurses

- Assist in investigating AEFIs (member of investigation team)
- Report results of investigation to Director/Manager of hospital and NIP Unit, CCHDC, Male
- Provide feedback to health workers on results of investigation and corrective actions to be taken
- Monitor for clustering events
- Inform Director/Manager immediately of deaths, hospitalization, clusters of events, events causing significant community concern
- Reassure the parents/ community
- Assist CSFP or other designated spokespersons to deal with media

Table 10: Administrative levels and activities at different levels

Administrative Level	Responsibilities and Activities	AEFI Classification Status
Peripheral Level	**AEFI clinical surveillance focal point with public health unit /immunization service provider level*** • AEFI detection and recording • Triage and reporting of non serious AEFI to Atoll level and national level regularly. Report serious AEFIs to National and Atoll level as soon as possible • Investigation of non serious AEFI initiated in coordination with atoll level and inform NIP • Corrective action • Public education/ communication	**Preliminary Classification** • Non-serious • Serious

Intermediate/Atoll Level	**Surveillance Unit at Atoll level - national Level (intermediate or Atoll level AEFI surveillance focal point and central level AEFI surveillance staff)**
	• Support Peripheral level
	  ○ Investigate non-serious AEFIs
	  ○ Coordinated with NIP/AEFI subcluster for investigation of serious AEFI under guidance of AEFI committee
	•
	• Causality Assessments of AEFIs guided by NIP and AEFI committee
	• Report to National AEFI Committee
	• Data analysis and search for additional cases
	• Corrective actions
	• Monitoring and supervision/training
	• Public education/ communication
		Provisional Classification of Serious AEFIs
		• For referral to national level
		  ○ Vaccine product related
		  ○ Vaccine quality defect
		  ○ Immunization error related
		  ○ Coincidental
		  ○ Immunization Anxiety related
		  ○ Unknown

National Level	**National program (NIP/MFDA)** • Provide expert support for field investigation • Guide Atoll level and peripheral level on causality assessment • Monitor information collection and assess serious AEFI • Causality Assessment of AEFI (Final - National AEFI committee) • Data analysis and search for signals • Recommend decisions for policy • Provide guidance on feedback to all levels	Final classification of all serious AEFI Maintain repository of all cases; serious and non-serious

	• Conduct research studies • Provide guidance on Monitoring/supervision & training • Define contents for Public education / Communication • At global level share/ obtain expertise and assistance	

Table 11: Structure of AEFI reporting unit at periphery

Locations	CSFP	PHU
Location : Atoll/regional/ Island health facility	Doctor /nurse	Health worker/nurse

Who should detect and report

The detection and reporting of AEFIs should be the responsibility of:

- AEFI detection:
  - Parents and other members of the community should notify the health care provider regarding AEFIs affecting their children and bring sick child to a health center or hospital
- AEFI notification:
  - Community health workers/nurses providing immunization services should report the AEFI and bring to the attention of the Clinical Surveillance Focal Point (CSFP) in the health care facility
  - Doctors, Nurses and paramedics providing clinical treatment of AEFIs in health centers and hospitals
- AEFI reporting

- Public health Unit with CSFP should report all AEFIs to NIP

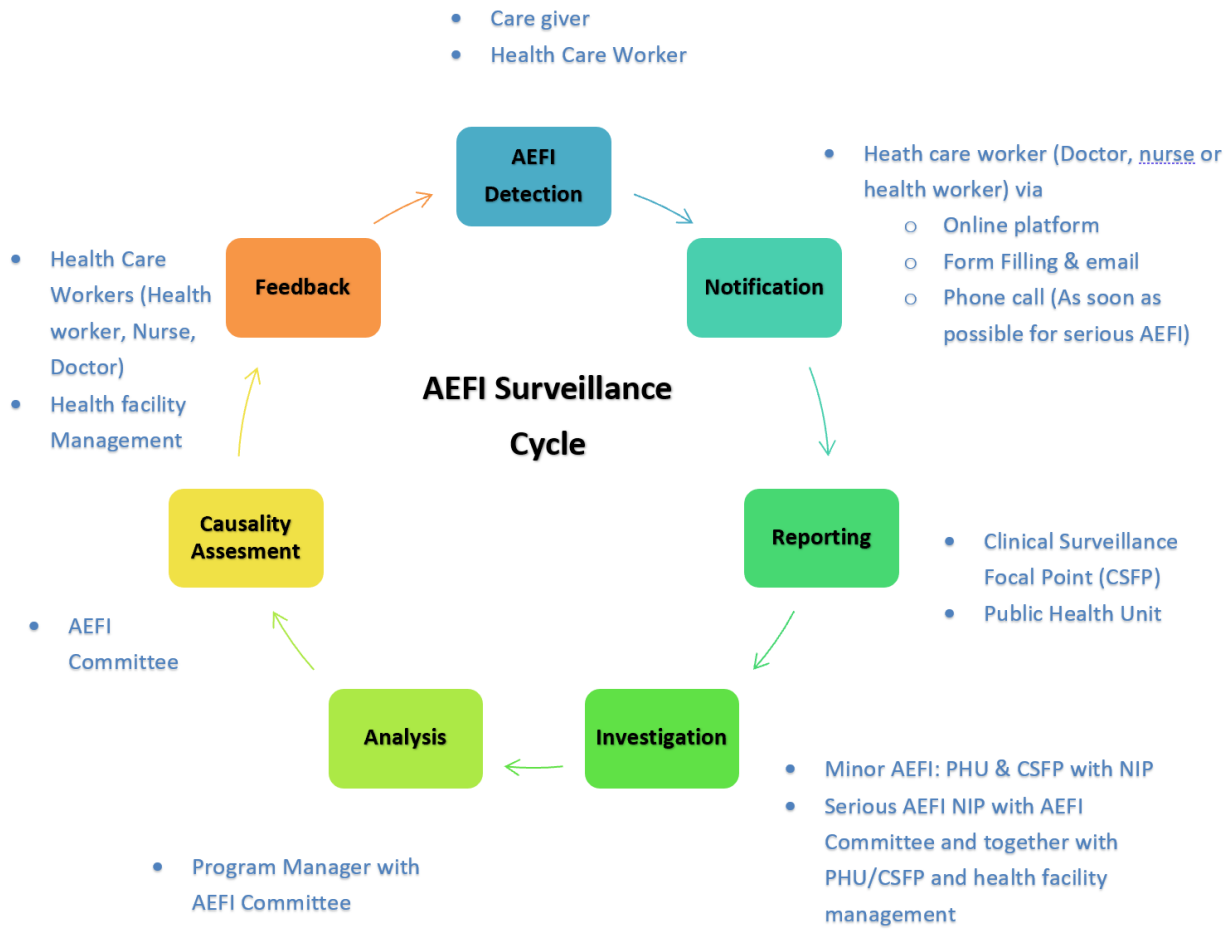


Figure 4: AEFI Surveillance Cycle

AEFI Reporting System:

AEFI surveillance should be carried out in all health facilities, (hospitals, health centres or immunization sites). Both private and government health facilities should be involved in reporting of AEFIs.

When, Whom and How to Report:

All health facilities should have identified focal points responsible for AEFI surveillance and reporting. These focal points are known as Clinical surveillance focal points (CSFP)

Information on AEFIs are reported from following sources:

- All community health workers in NIP session or during house visits may detect or parents notify regarding AEFI cases and report to Public Health Unit or to clinical surveillance focal point (CSFP).
- Hospital/Health Facility: All designated hospitals and health facilities will report AEFI cases from inpatient and outpatient department (OPD) services: In OPD it is the responsibility of treating Medical Officer (MO) to report AEFI. In high workload setting, MO/OPD may refer the case to Clinical surveillance focal point.
- Private/NGO clinics providing immunization services will report to respective Director/ Manager/ Medical Officer of Hospital/Health Facilities (For this purpose, AEFI reporting form should be made available to these clinics)

Reporting Form and reporting timeline:

- Routine AEFI surveillance report form should be filled properly including the name of the reporting health care personnel, the institute with details of AEFI including short relevant clinical history and examination.
- AEFIs; the trigger events (serious AEFI, death, hospitalization and AEFIs causing community concerns) are also included. Serious AEFIs and unusual events should be reported to the NIP unit immediately and complete AEFI form within 24 hours. Minor AEFI maybe reported within 48 hours.
- Report weekly AEFI and a compilation of monthly AEFIs at the end the month. if there are no cases, zero must be reported
- Upon receiving the routine weekly and monthly AEFI surveillance focal point in NIP, should review it and log it.
- At central level AEFI should be regularly analysed, weekly

Table 12: Core Variables with Minimum Information Required for Reporting in AEFI surveillance

	Suggested Heading	Description of the Basic core variable
Identify	Date AEFI report first received at National level	Date when information of the AEFI case first reached the National level
	Country where the AEFI occurred	Name of the country where the adverse event occurred
	Location (address)	Geographic location of the case (address)
	Unique identification of the report	Unique id number used for communicating the details of the case
Case	*Patient identifier*	Name of the patient or initials as decided by the country
	Date of birth (or)	Date patient was born
	Age at time of onset (or)	Age at time of onset
	Age Group at onset	Age Group (<1 year, 1-5years, >5 years)
	Sex	Male or Female
	Medical history	Free text information (e.g. allergies, concomitant medication etc.)
Vaccine	*Primary suspect vaccine name*	Vaccine suspected to have caused the AEFI
	Other vaccines given just prior to AEFI	Other vaccines given prior to the AEFI
	Vaccine batch/lot number	Batch/lot number of all vaccines mentioned above
	Vaccine dose number for the vaccinee	Dose number for this particular vaccinee
	Diluent batch/lot number	Batch/lot number of the diluent (if applicable)
Event	*Date and Time of vaccination*	Date and time the vaccine was administered
	Date and Time of AEFI onset	Date and time of the AEFI onset
	Adverse event	Case diagnosis + Signs & Symptoms
	Outcome of AEFI	Outcome of the reaction(s): Recovering/resolving; Recovered/resolved; Recovered/resolved with sequelae; Not recovered/not resolved; Fatal; Unknown
	Serious case	If the case is serious and resulted in death, threatened the patient's life, caused persistent or significant disability, hospitalization, congenital anomaly or any other medically relevant event that may jeopardize the patient or may require intervention to prevent one of the outcomes mentioned here
Reporter	Name of initial reporter of AEFI case	Name of the reporter of the AEFI case
	Institution/Location	Place (address) of the reporter (including the name of the country)
	Position/Department	Reporter's designation & section of work
	E-mail address	Reporter's e-mail address
	Telephone	Reporter's phone number
	Date of report	Date when the report was compiled by the reporter
Other	Comments (if any)	Additional details about the case in free text (including documents/ attachments)

IMPORTANT: *Critical variables in italics*

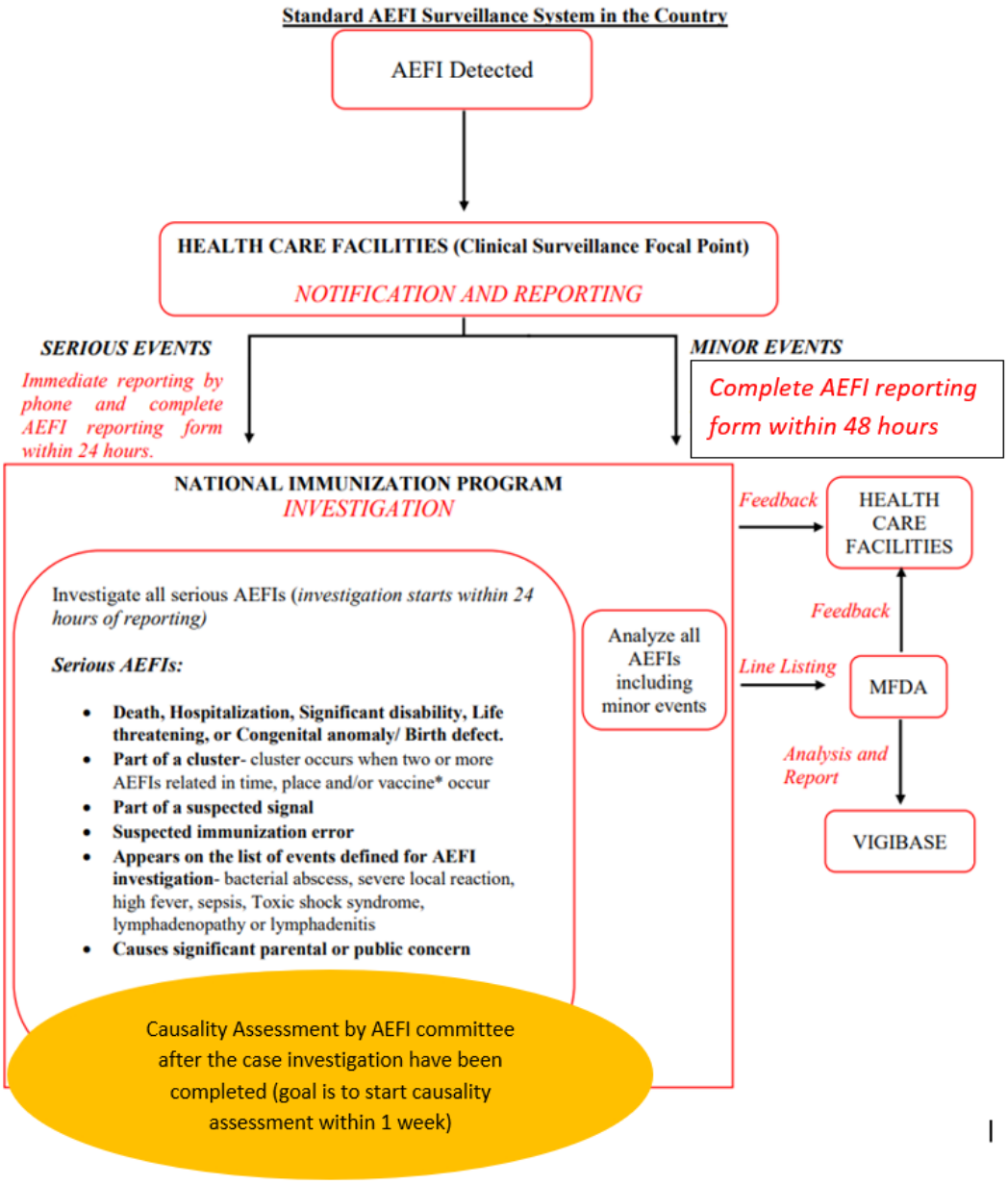


Figure 5: AEFI surveillance system

Encouraging Health Workers Reporting

The support of field staff is crucial for the success of any surveillance programme. Field workers are encouraged to report adverse events without fear of penalty. The aim is to improve the health care system or provide further training and not to blame individuals.

In order to encourage reporting the manager (e.g. Specialized Doctors, Nurses, or Medical Officers) is responsible to carry out the following activities:

- Train staff on AEFI and its reporting
- Increase awareness of health staff on importance of reporting
- Give positive feedback and appreciation for reporting. It is essential that health workers be given feedback about the results of investigations and any actions taken as a result of the report

The type of feedback that is given and the manner in which it is given depends on the audience. Managers should ensure that there is an ample supply of reporting and investigation forms in their institutions in order to facilitate timely reporting.

Barriers to reporting Immunization service providers may not report AEFI for a number of reasons, such as:

- considering that the event did not occur after immunization (however, all events following immunization as per the definition should be reported);
- lack of knowledge about the reporting system and process;
- apathy, procrastination, lack of interest or time, inability to find the reporting form;
- fear that the report will lead to personal consequences; n guilt about having caused harm and being held responsible for the event; and n diffidence about reporting an event when not confident about the diagnosis.

It is worth emphasizing that, unless immunization service providers/units at community level generate and process reports appropriately, an adequate immunization safety surveillance system will not exist. Staff must be encouraged to report adverse events without fear of penalty. The aim is to improve systems or provide further training, and not to blame individuals. Positive feedback to health workers is essential. The feedback should include the outcome of investigations or causality assessment when these are carried out, and recommendations on the management of the vaccinee, particularly with regard to the need for future vaccination. There must be an adequate supply of reporting forms. Pre-addressed and postage-paid forms may improve reporting in some countries, especially from private physicians.

Private-sector reporting As in government institutions, all private-sector medical institutions handling immunization services and treating AEFI cases should report all AEFI to the respective immunization

safety surveillance focal points or national pharmacovigilance centres. Reporting from the private sector is encouraged for two reasons: n Individuals seek medical care from the private sector, following vaccines received at public institutions. n It is important to monitor vaccines used in the private sector and, therefore, reporting all AEFI is necessary. To maintain uniformity of reporting data, AEFI reporting forms used in the AEFI surveillance system should be made available to the private sector as well.

Investigating AEFIs

A case investigation is usually the first major action to be taken when an AEFI is reported and should begin without delay. Investigation should be initiated by the health workers who detects the AEFI or by the Clinical Surveillance Focal Point or by the doctor/nurse who sees the case in health facility/hospital. With inadequate or incomplete data, an AEFI can be deemed either ineligible for causality assessment or unclassifiable.

Purpose of an investigation

The ultimate goal of a case investigation is to find the cause whether the vaccine or immunization process is responsible for the reported AEFI or to find another reason and correct it if possible and reassure the public. The purposes of investigating AEFI cases are following:

1. To confirm diagnosis of a reported AEFI and clarify the outcome of the event
2. To identify link between the vaccine administered and the AEFI
3. To examine the operational aspects of the programme to the reported AEFI
4. To determine whether a reported event was a single incident or one of a cluster
5. To determine cause of the AEFI so as to provide the best intervention/medical care and take any further action deemed necessary
6. To determine whether un-immunized people are experiencing the same medical events

If the cause is identified as programme error, problem should be corrected quickly. If an AEFI is found to be coincidental, then the community can be reassured about the safety of the vaccine and the immunization programme. The act of investigating AEFI increases the confidence of the community in the health care system and the immunization programme in particular.

What should be investigated immediately?

Managers should ensure that their staff monitor and report an agreed list of adverse events. Health workers should know to monitor and report at least the following “triggers” events immediately.

The following AEFIs must be reported and investigated:

1. All clustering of any AEFI
2. All deaths that are believed by health workers, or the public, to be related to immunization.
3. All cases requiring hospitalizations that are believed by health workers, or the public, to be related to immunization.
4. All severe or unusual medical events about which health workers, or the public are concerned to be related to immunization.

The above 4 types of events are called trigger events because they stimulate or trigger a response, such as investigation and corrective actions.

Cluster of AEFI

A cluster is defined as two or more cases of the same adverse events, which are related in time, and have occurred within the same geographical unit (Atoll, Island, Community) or associated with the same vaccine (same batch/lot number) administered or same vaccination site. For example, two or more cases of abscess occur following one immunization session in a community; repeated abscess cases following immunization by same vaccinator.

When should Investigation be started?

AEFIs those have resulted in death, hospitalization, and widespread community concern, or cluster, investigation should begin as soon as possible, ideally within 24 hours of detection. When an investigation is believed necessary, it is important to initiate investigation immediately to identify any programme errors that might be present and to correct them before other people are exposed to the same error and to assure community that their health and concerns are taken seriously.

Who should investigate?

In most cases, a preliminary investigation will be made by the community health workers, physician, nurse who detect the case in a health center/hospital. In case of death, hospitalization, cluster event, and event causing significant parental/community concern, Medical Officer, Nurse / Clinical surveillance focal person (CSFP) will initiate investigation and notify to the National Immunization Programme. The detail investigation will be carried out by a team. National AEFI committee will coordinate the investigation and causality assessment.

Team Members for Investigation: at island and Atoll levels

A team comprising of the following members will investigate AEFI (guided by the central NIP and AEFI committe)

1) Clinical AEFI surveillance focal point
2) Public health unit
3) Quality Improvement Department (if available)
4) A medical consultant and/or Pediatrician (and / or other specialities as required)

5) May consider to add nursing in charge and or Medical in charge / Medical director

If all members of the team are not available, at least 2 members could start the investigation and one of them must be a doctor. They will call upon and ask the advice of any other member of the proposed team as and when needed. The medical director and nurse in charge of the health facility or hospital would need to be informed about the progress of investigation even if they are not in the main investigation team.

National level investigation team with AEFI committee

The Public Health Programme Manager-NIP will initiate investigation if clusters are detected at national level or any AEFI with National NIP programme concern. A national level investigation team may be formed to investigate national level and support sub-national investigation team to investigate trigger events with the following members (if necessary). During AEFI investigation the concerned authorities such as MFDA, QID MOH should be informed, even if they may not be in the main case investigation teams. Suggested team members include;

1. Public Health Specialist
2. Representative from Maldives Food and Drug Authority
3. Clinician (Pediatrician/ Physician or other speciality as required)
4. Nurse
5. A member from Quality Control
6. Representative from partner agencies such as WHO and UNICEF can be on the panel as ex-officio members and may be invited, when required
7. Regional / Atoll Focal Points, can be on the panel as ex-officio members and may be invited, when required

Role of AEFI Investigation Team

- Conduct AEFI case investigation
- Provide AEFI investigation report with findings and conclusions
- Assist with communication in case of crisis
- Recommend corrective action to be taken by appropriate authority
- Causality assessment (AEFI committee)

How to Investigate:

It is essential to investigate adverse events completely and without any delay. The investigators should search for system problems rather than finding individuals to blame. While an individual may have been at fault, it is more effective to concentrate on changing the system/procedures to

avoid such errors than to blame or punish any individuals. Such an approach is essential to ensure that AEFI reports are encouraged. During investigation the investigators will gather information from the person.

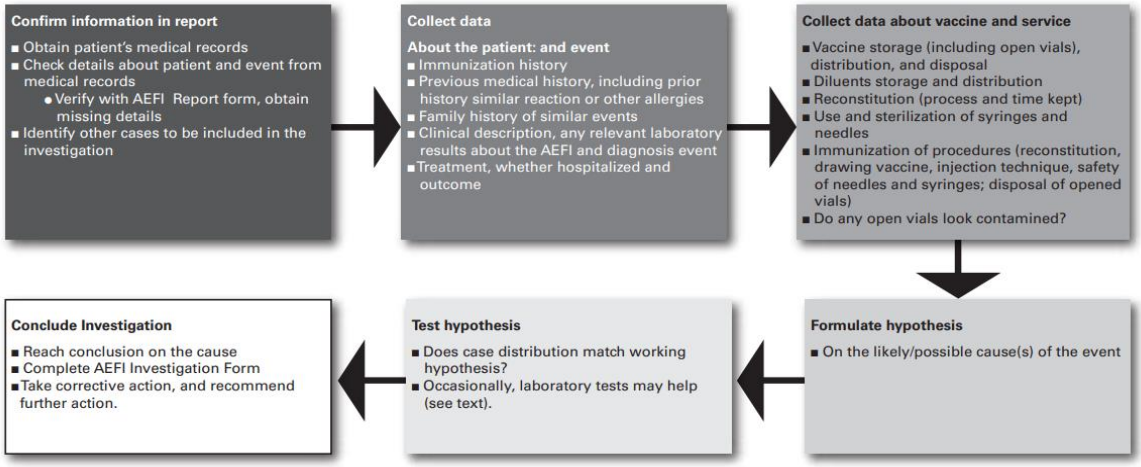


Figure 6: Steps in AEFI Investigation

- AEFI Patients: Patient should be examined and all available medical records should be reviewed
- Health workers, nurses and supervisors: Health workers/nurses who gave vaccine during the suspected session should be interviewed. Supervisors should be asked about immunization practice of the same health workers/nurse.
- Besides interview, it is important to observe a session of the same health worker because it might reveal the cause, since bad practice may be repeated.
- Clinicians who have treated the patient
- Community members: Investigators should talk to parents and others who were present during the suspected vaccination session about what they might have seen. Those who received vaccine on the same session should also be examine if necessary.

Note: It is not recommended all members of the investigation team to visit to the field as it may cause unnecessary concern by the public. Field investigation is the responsibility of Medical Officer/Nurses.

Key data to be collected

1. Data on each patient
   - demographic data: patient name, date of birth, age, sex, address
   - history of present illness – symptoms, appeared and its duration, treatment, outcome, diagnosis
   - history of past illness e.g. any reaction to previous doses, drug or other allergies, family history

- pre-existing neurological disorders, current medications
- immunization history- vaccine, number of doses received, date and place of last vaccination, site of injection
- laboratory results about blood, stool, or other samples, if appropriate
- Autopsy report with toxicological screening and/or histo-pathological analysis in case of death, if available.

2. Data about the vaccine(s) and diluents administered to the patient
   - batch number
   - Expiry date
   - Manufacturer
   - When and from where vaccine was sent
   - Laboratory results about vaccine, if appropriate

3. Immunization Programme related data
   - common practices followed for
     - Storing vaccines and diluents; are frozen / expired vaccines used?
     - handling vaccines during and after session
     - practices in reconstituting vaccines - time of reconstitution, correct / sterile diluent
     - giving immunizations - correct dose, right route and right place
     - time of disposal of vaccine vials
     - availability of needles and syringes
4. Data on other people in the area
   - Number of people who received immunization from the same lot and in the same immunization session or both and number of those who fell ill and their symptoms (Complete a separate AEFI case investigation form for each AEFI case)
   - Number of unvaccinated people who fell ill with similar symptoms.
5. Name of Health care worker/ nurse who gave immunization and what type of training received from NIP

How a cause is determined?

Until the investigation is complete, a "working hypothesis" should be formulated after collecting sufficient information as to what was the probable cause of the AEFI. Causes of AEFIs are classified in four ways, for example

Immunization error related AEFI

- Error in vaccine and diluent handling
- Error in vaccine prescribing or non-adherence to recommendations for use
- Error in administration

Vaccine product related and vaccine quality defect related Reactions

- Reaction associated with the route and/or site of administration of the vaccine or vaccine specific characteristics
- Immune-mediated vaccine reactions
- Consequence of replication of vaccine-associated microbial agent(s) in the vaccine or a close contact of the vaccine
- Direct toxic effect of vaccine component or contaminant (e.g. quality defect)

Immunization anxiety related AEFI (fear of injection)

Range of symptoms and signs that may arise around immunization that are related to "anxiety" and not to the vaccine product, a defect in the quality of the vaccine or an error of the immunization programme.

Coincidental (unrelated to immunizations or vaccines)

The focus of investigation is to confirm the working hypothesis. No action should be taken based on the hypothesis, until it is confirmed with reasonable certainty. It is the responsibility of investigation team to form, test and confirm /discard the working hypothesis in a scientific manner.

Collect and Dispatch Specimen:

Laboratory testing:

Human specimens For biochemical, histopathological and microbiological examination, specimens should be processed at the local hospital. In case facilities are unavailable locally, specimens should be forwarded to the most suitable laboratory in the country or even an accredited laboratory abroad if warranted

The investigation team should decide whether specimens are required to confirm or rule out the suspected cause. Only appropriate specimens necessary for investigation should be collected, and investigation team should contact the National Health Laboratory (NHL) and get advice on specimen collection, transport etc., well before the specimen collection and dispatch.

Notes on specimen taking:

1. Specimen from the patient
    - blood, urine, CSF, swab from wound/abscess site as appropriate
    - autopsy specimens (if death occurred) as above, plus tissue samples for toxicological screening (liver, brain, kidney and stomach content or section of stomach) and tissue samples for histo-pathological screening (brain with meninges, lung, adrenal glands as well as any other organ in which pathology is suspected)

A good communication among clinician, laboratory and investigation team is important to make a good decision on what specimens to be collected and where to be sent for investigation etc.

2. Vaccine, diluents in use at the vaccination center
    - collect the actual opened vial of vaccine(s) and diluents used to vaccinate the child (ren) who suffered from AEFI
    - collect some unopened vials of the same lot of vaccine and diluents from the same manufacturer from health center, local island store as well as from the Atoll store
3. Syringes
    - If located, all syringes should be capped with extreme caution. It will may not be possible to locate the syringe by which the patient was vaccinated
    - Collect a sample of unopened AD syringe and disposable syringes

Table 13: Guide to Human Specimen Collection Following Selected AEFI

Hypothesis	Specimen	Reason	Specimen collection
Suspected bacterial sepsis due to contaminated vial, needle contamination, coincidental	Whole blood	Bacterial culture	Blood 8-10 mL in each of 2 blood culture bottles.
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
Suspected viraemia due to vaccine virus or coincidental disease	Serum	IgM and IgG antibodies for viral pathogens	Clotted blood 5-10 mls
	CSF	Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other)	Sterile container Viral culture media
	Skin vesicle	Viral culture	Sterile container Viral culture media
Suspected anaphylaxis	Serum	Mast cell tryptase Specific IgE	Clotted blood 5–10 mL Clotted blood 5-10 mL
Suspected toxin or drug injection/ingestion, either programme error or coincidental	Urine	Drug screen	Sterile container 1 mL
	Blood	Chemistry when indicated, liver enzymes, glucose, electrolytes	Clotted blood or in Li Heparin 5-10 mL
Suspected VAPP or coincidental encephalitis	Stool	Enterovirus and viral culture	Sterile container

The vaccine and diluents may be tested for sterility and composition and the syringes for sterility. Testing should be requested on a clear suspicion and not as routine, and never before the working hypothesis has been formulated.

Notes on Dispatch Specimen by CSFP:

- All specimens (human specimens, vaccines, diluents or syringes) should be labeled and sealed in containers or plastics bags
- Specimens should be transported on ice (separate vaccine carrier) to the National Health Laboratory for toxicological screening and with formalin or any other medium for histo-pathological analysis as instructed by laboratory
- Be sure the transport time is less than the cold life of the ice.
- CSFP will attach a copy of the case investigation form in a separate envelope to help laboratory perform the correct tests as well as the request form to perform tests.

Again, it is recommended investigation team to contact the national health laboratory and get advice on specimen collection, transport etc., well before the specimen collection and dispatch.

Vaccine Laboratory testing may sometimes confirm or exclude the suspected cause. However, testing should be requested on the basis of clear suspicion and not as a routine procedure, and never before the working hypothesis has been formulated. Laboratory testing is always costly. It is important to note that there is a need for a good laboratory network (including the manufacturers) to support immunization safety surveillance. Determination of which samples to test, if any, depends on the working hypothesis for the cause of the event. The vaccine may be tested for sterility, toxicity and content (e.g. aluminium content); the diluent for sterility and chemical composition; and the needles and syringe for sterility. It is important to monitor the cold chain of vaccine vials under suspicion, irrespective of whether they need laboratory testing or not.

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. Apart from checking on these three factors, the investigator should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease. Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition. The investigation should promptly characterize all known cases and research similar ones (Figure 3). Cluster identification (i.e. cases with common characteristics) is done by gathering details (who, when and where) of vaccines administered. This can be achieved by collecting and recording n detailed data on each patient; n programme-related data (storage and handling, etc.); and n immunization practices and the relevant health workers' practices. Common exposures among the cases can be identified by reviewing: n all data on vaccine(s) used (name, lot number, etc.); n data on other people in the area (also non-exposed); and n any potentially coincident factors in the community. 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 or an immunization error-related AEFI. For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction (i.e. a signal). Awareness of 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.

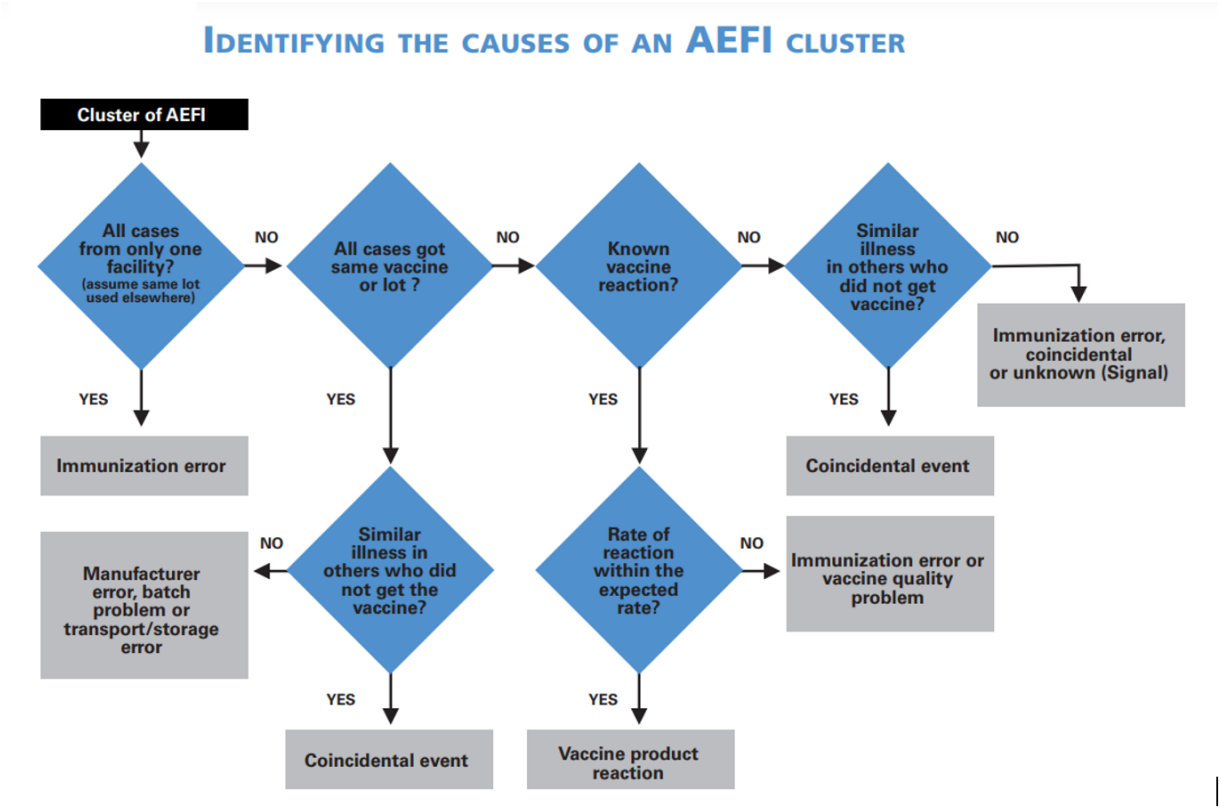


Figure 7: Identifying the Cause of AEFI Cluster

If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine or the respective lot is likely. If the event is a known vaccine reaction but is found to occur at an increased rate, an immunization error or a vaccine problem are likely causes. Finally, if cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group, the adverse event was probably coincidental.

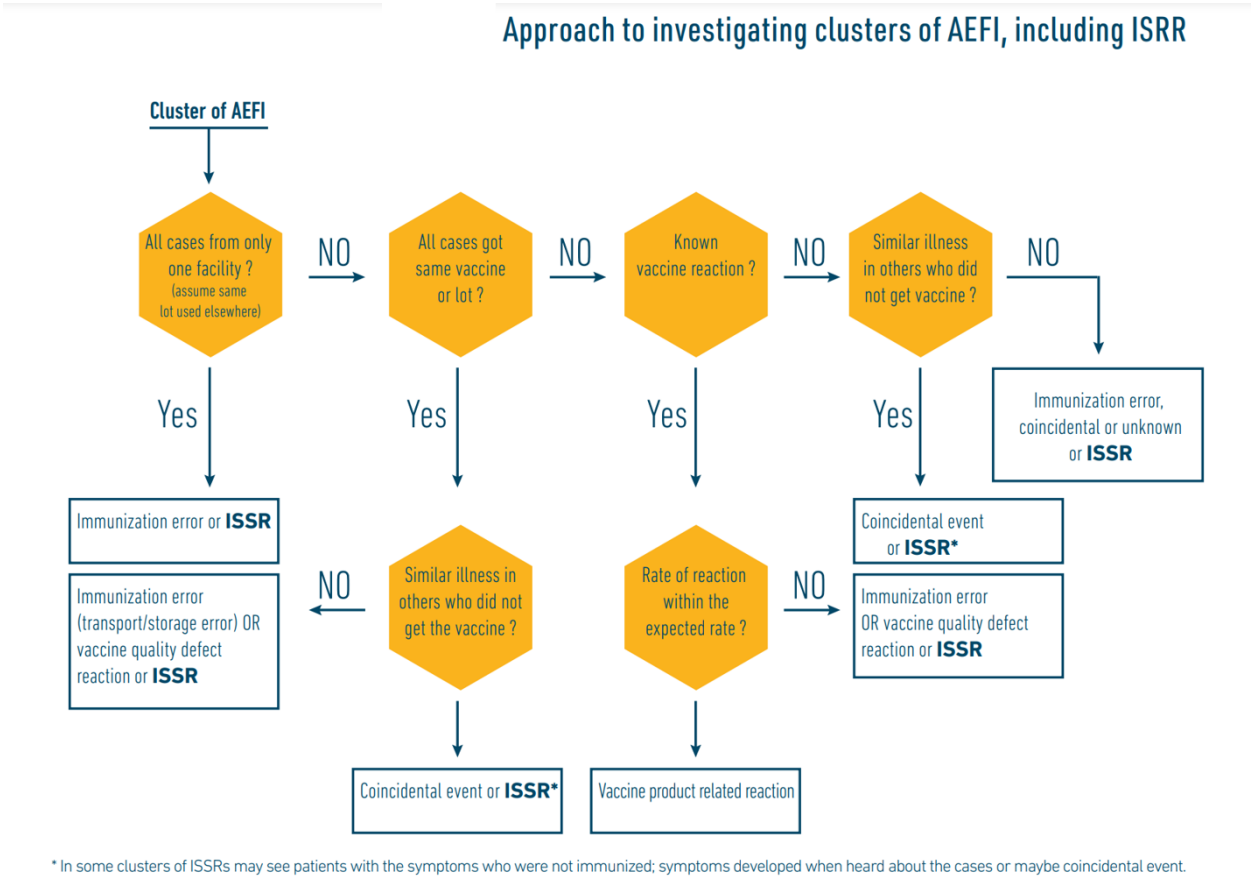


Figure 8: Approach to Investigation clusters of AEFI, including ISRR

Table 14: Cause-Specific Cluster Characteristics

CAUSE-SPECIFIC CLUSTER CHARACTERISTICS

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 who were not immunized
Immunization anxiety-related reaction	Clusters of fainting after immunization are well-recognized as anxiety-related reactions during immunization programmes targeting adolescent girls

In a cluster analysis, if a previously unknown event is reported only among the vaccinated group, it can be a potential signal provided that both immunization error-related reactions and coincidental events are excluded. Such AEFI require comprehensive assessment and further studies to understand their true causality.

Investigation of deaths

A field investigation of a death following immunization has to be conducted without delay as the death can cause significant community concern (Table 13). All administrative levels, including the national immunization programme, should be notified of the death. It is recommended that death investigation should be carried out by a team comprising clinical, laboratory and forensic experts. The team should be supported by the programme managers. All relevant information on the event should be available to the investigation team. An autopsy is preferred and is recommended following all deaths suspected to be caused by vaccine or immunization. However, the decision to conduct the autopsy should be taken within the context of religious, cultural and the legal framework of the country. At the time of autopsy, the autopsy surgeon should be provided documents outlining detailed preclinical and clinical history, including laboratory and radiological findings. Where possible, a visit to the scene of the death to gather additional evidence; radiological examination; histopathological examination; and toxicological and microbiological examinations will be useful. Samples for microbiology, immunology, histopathology, and virology should be collected according to the instructions given by the relevant laboratories. Adherence to a standard autopsy protocol which allows for a comprehensive causality assessment of a reported

death following immunization is important and necessary. If an autopsy is not possible, a verbal autopsy can be carried out in accordance with established guidelines and protocols. WHO protocols for verbal autopsy standards are a useful reference.

ACTIONS TO SAFEGUARD THE PUBLIC DURING AN INVESTIGATION

Stage of investigation	Actions
Incident detected	■ Assess and investigate with an appropriate degree of urgency ■ Possibly quarantine suspect vaccines and take other immediate counter actions, as appropriate ■ Begin communication with all concerned parties
Investigation starts	■ Ensure that the investigator has adequate resources, and provide more if needed ■ Increase surveillance to identify similar cases in and out of area: sometime enhanced or active surveillance is required to gather more information/data Define any suspect vaccine ■ Maintain continued communication on progress of the investigation with all concerned parties: do not suggest any hypothesis
Investigator develops working hypothesis	■ Do not communicate the working hypothesis until confirmed (the working hypothesis is for the investigation team only and not for the public since, if the investigation reveals something different from the working hypothesis, this may affect public trust) ■ If programme-related errors are the working hypothesis, correct them ■ If a vaccine problem is suspected, quarantine suspect vaccines
Investigator confirms working hypothesis	■ Advise the community of the cause and the planned response ■ Communicate with all concerned parties on findings

Analysis of AEFI Reports

Analyzing of data on AEFI consists of reviewing the case investigation report for each patient, reviewing other data about the event and the community in which it took place, making a final diagnosis and identifying the probable cause.

The progress in AEFI surveillance can also be monitored by analyzing the reports as follows:

- Number of AEFI reports received annually from community and from health facility
- Number of AEFI by different levels (By Atoll, Islands etc.,)
- Number of AEFI by type (i.e, trigger events; number of deaths, number of abscess etc
- Number of AEFI by type and level (number of deaths by Atoll, number of abscess by Islands etc.,)
- Number of AEFI by antigen
- Total number of AEFI by antigen (total AEFI for Penta, total AEFI for Measles etc)
- Each Type of AEFI by antigen (number of deaths by Penta, number of deaths by Measles, number of abscess by Penta etc.,)
- Classification of events by cause: programme error, vaccine induced reactions, coincidental, or unknown
- Unusually severe AEFIs

Analysis of data on AEFI should consider the following:

- Reporting source (reports of AEFI by different sources may provide a wider range of information);
- Completeness of submitted AEFI forms; n verification and reassurance of data accuracy;
- Identifying health institutions where AEFI are not reported (determining whether this is due to failure of reporting or whether there are no AEFI to be reported) and checking on “zero reporting” or “nil reporting”;
- Performance of causality assessment to classify the AEFI;
- Estimated AEFI reporting rates (assessing the number of reported AEFI and the rate per 1000, 10 000 or 100 000 doses of vaccine used in a specified time period);
- Estimated rates by type of AEFI and by antigen (assessing the number of cause specific reported AEFI and the rate for 1000, 10 000 or 100 000 doses of vaccine used in a specified time period); n comparison of these observable rates with available or expected known events, whether vaccine reactions or background rates or historic reporting trends.

It is encouraged to analyzed data only by absolute numbers or proportions (percentages), but in rates too, where comparison is more valid and necessary.

E.g. Incidence of Abscess per 100,000 doses of Pentavalent vaccine

How to calculate this?

Incidence of Abscess for Pentavalent in Atoll 'Y"

$$= \frac{\text{Number of Abscess reported following penta vaccine in Atoll 'Y'}}{\text{Total Number of penta vaccine given in Atoll 'Y' during a given time period}} \times 100{,}000$$

In Atoll the Director/Manager of Hospital will analyze the reports of all AEFIs on monthly basis and provide feedback to respective Island. If there is any unusual high rate of AEFI he/she should inform respective Medical Officer/Nurse to look into the matter and take appropriate action. Clinical Surveillance Focal Point will assist Director/Manager in analyzing the AEFIs.

The Medical Officer/Nurse of Islands will analyze the reports of all AEFIs on monthly basis and provide feedback to the Community health Workers/Vaccinator Nurses. If there is any unusual high rate of AEFI he/she should look into the matter and take appropriate action. LSO will assist Medical Officer in analyzing the AEFIs.

NIP Unit will also analyze the reports of all AEFIs on monthly basis and provide feedback to

Director/Manager, MFDA, NHL and other partner Agencies (WHO, UNICEF etc)

Indicators used for Evaluation of AEFI Surveillance:

The indicators for evaluating AEFI surveillance should be evaluated regularly to determine its effectiveness. The following indicators are used to evaluate the surveillance system:

- **Timeliness, completeness and accuracy of routine AEFI surveillance reports;** every month the monthly AEFI surveillance report should be received by the Atolls from the Islands and in turn by the central NIP Unit. The date on which the reports are received is timeliness and reports from all designated units are the completeness.

✓ At national, Atoll and Island level

- **Swiftness (Timeliness and completeness) with which case investigation begins after a trigger event is reported;** whether the AEFI was reported within 24 hours of detection and whether an investigation was begun within 48 hours after the report was received.

✓ At national, Atoll and Island level

- **Appropriateness of actions taken to avoid further programme errors;** after reviewing the case investigation and reports, the actions proposed for the elimination of programme errors are adequate.

✓ At national, Atoll and Island level

- **Increase in immunization programme participation:** AEFI surveillance should result in increase immunization coverage. The extent of coverage can be measured by evaluating AEFI surveillance report, yearly AEFI report and coverage data.

Who should analyse the data?

Data analysis could be carried out at different levels of the immunization safety surveillance system: the programme implementation level, the subnational level and the national level. The extent and purposes of analysis will vary at each level. Analysis of data at the service provider level is very important for identifying immunization errors and ensuring that corrective action is carried out in a timely manner. Data analysis at higher levels with larger denominators is important to identify rare vaccine safety events and also detect signals.

Table 15: Purpose of Data Analysis at Different Levels

PURPOSE OF DATA ANALYSIS AT DIFFERENT LEVELS

Programme implementation level	What data to analyse	Purpose of data analysis at given level
Local level (immunization provision level)	Number of reports by clinics, hospitals, villages by a given time	These are programme operation/surveillance performance indicators (timeliness, completeness).
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Reported AEFI by antigen	Will also identify vaccine reactions and coincidence.
Subnational level (regional/ provincial/ district/ town)	Number of reports by local levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at local level.
	Reported AEFI by place (clinics, hospitals), persons and time	Identification of immunization error-related events will lead to corrective action.
	Cluster analysis	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Reported AEFI by antigen	Will identify vaccine reactions and coincidence.
National level	Number of reports by intermediate levels	These are programme operation/surveillance performance indicators (timeliness, completeness) at intermediate level.
	Reported AEFI by place (clinics, hospitals), persons and time	Cluster analysis leads to identification of immunization error related events, coincidence and vaccine reactions.
	Cluster analysis	Will identify vaccine reactions, including detection of signals.
	Reported AEFI by antigen	Leads to operational and policy decisions being taken in the country.

How should the data be analysed and interpreted?

Step 1: Following verification of cases, all reported AEFI data should be line-listed and/ or entered into a database. Line-listing will help initial identification of clustering or any unusual or significant reporting events that need further analysis (Annex 4).

Step 2: AEFI data should be tabulated by place, person, time, antigens and type of event (e.g. high fever, abscess). This step further filters the AEFI by different variables and helps programme managers to generate clues for further analysis. Even at this step, it is possible to identify common immunization errors. For example, an increased number of abscesses by one immunization centre is more likely to be due to immunization-related error. However, further investigation is necessary to confirm causality.

Step 3: AEFI rates should be calculated. The number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (month, quarter-year or year). Analysis should be expanded to include AEFI rates by first, second or third dose if the antigen is administered more than once. For this, the number of doses administered of the given antigen – by first, second or third dose should be used as the denominator.

Step 4: Rates should be compared and interpreted. Expected vaccine reaction rates that are available for each type of AEFI and antigen (WHO vaccine reaction information sheets) provide a guide to decision-making on corrective action for reported AEFI. It is also important to know the background rates of reported medical events in the country. Background rates are independent and are not related to the vaccine. Observed (reported) rates include both background rates and vaccine-related rates. Comparison of background rates with reported (observed) rates of AEFI will provide support for a conclusion on the causality of these events being due to a vaccine reaction. Vaccine reaction rates are further divided into two subcategories: expected vaccine reaction rates and excess vaccine reaction rates. The WHO vaccine reaction information sheets give the “expected” vaccine reaction rates), which are based on pre-licensure and post-licensure data. These expected vaccine reaction rates are known rates due to the inherent properties of the vaccines and the response by recipients. If the value exceeds the “expected” vaccine reaction rates, one should consider whether this is a true increase in the vaccine reaction rate or if the values are due to other factors. In addition, these reported vaccine reaction rates depend on the reporting source – such as type of surveillance (active, passive, enhanced passive), special studies etc.

Table 16: Factors to Consider When Comparing Rates of AEFI

FACTORS TO CONSIDER WHEN COMPARING RATES OF AEFI

Vaccines
Although a vaccine may have the same antigens as another, different manufacturers may produce vaccines (or lots of the same vaccine) that differ substantially in their composition, including the presence (or not) of an adjuvant or other components. These variations result in vaccines with different reactogenicity (the ability to cause vaccine reactions) which in turn affects the comparison of vaccine-attributable rates.

Age
The same vaccine given to different age groups may result in different vaccine-attributable rates. For example, MMR vaccine given to infants may cause febrile convulsions. This symptom does not occur in adolescents who are given the same vaccine.

Vaccine dose
The same vaccine given as a primary dose may have a different reactogenicity profile than when it is given as a booster dose. For example, the DTaP vaccine given as a primary dose is less likely to result in extensive limb swelling when compared with the same vaccine given as a booster dose.

Case definition
Adverse events may be defined differently in surveillance/research studies that do not use the same case definition. Not using standardized case definitions may consequently affect the estimation of the AEFI rate. The Brighton Collaboration has developed case definitions for many vaccine reactions (www.brightoncollaboration.org).

Time period
It is important that estimates of AEFI rates are limited to a given time period (e.g. quarterly, annually) to enable a valid comparison to be made. This is helpful when interpreting AEFI rates due to possible vaccine reactions or coincidental events. It also adds to the validity of the rates as the denominator (vaccine doses administered in a given time period) contributes to more accurate estimates.

Surveillance methods
The way that surveillance data are collected may alter the rate. For example, surveillance data may be collected actively or passively, using pre-licensure or post-licensure clinical trials, with or without randomization and placebo controls.

Background conditions
The background rate of certain events may differ between communities. This can influence the observed rate even though the vaccine-attributable rate is the same in both communities. For instance, reports of death post-vaccination may be higher in a country that has a higher background rate of deaths due to coincidental infections.

In the scenario presented here, we can compare the observed rate of 0.44% febrile seizures reported in country A with the expected rate of febrile seizures following measles-containing vaccines, which is 0.03%. Thus the observed (reported) rate of 0.44% is greater than the expected vaccine reaction rate of 0.03% and therefore warrants investigation. We ask ourselves whether the case definition is correct, whether the onset interval concurs with the interval of the reported febrile seizures cases after vaccination or if something is wrong with the vaccine product. In any analysis of vaccine adverse events, confounders or sources of bias that should be considered include (but are not limited to) age, gender, race/ethnicity, season (e.g. for influenza vaccines) and country/region. At the international level, data

analysis aims mainly to identify the signals and compare pre-licensure and post-licensure safety data, and to share the findings with countries to support the decision-making. The data analysis also helps manufacturers to ensure vaccine safety during production of vaccines.

How should a cause be determined?

Until the investigation is complete a working hypothesis is all that can be formulated. Later it will be possible to analyse the data, assign a cause and classify it in one of the categories of AEFI. For a few medical events, the diagnosis itself will show whether the cause is immunization error-related, vaccine-related, coincidental or an injection reaction. In other cases, additional information and evidence may be required to identify the cause. Comparing background data with reported (observed) data does not conclude the search for causality. It only generates the hypothesis. To conclude that a vaccine causes a particular vaccine reaction, it is necessary to demonstrate that the risk in vaccinated individuals is greater than that in non-vaccinated persons, provided that the effects of confounders and bias are ruled out. Estimating relative risk and attributable risk is necessary, and retrospective or prospective analysis of available data or the design of epidemiological studies (case series, case-control cohort studies) will strengthen the conclusion of causality.

Taking Action in Response to AEFI

AEFI detection, investigation and analysis must lead to action to keep credibility of immunization program high. The following actions need to be taken after an AEFI:

- Health workers must know how to diagnose serious AEFI
- Treatment must be the first response to an AEFI
- Timely reporting to appropriate level; serious AEFI should be reported at once
- Communication with patients and other members of the community
- Communication with media (if necessary, by authorized persons only)
- Ensuring continuation of the Programme: It is never appropriate to discontinue the immunization programme while awaiting the completion of investigation.
- However, corrective actions after completion of investigation are essential.

However, health workers may be reluctant to report serious AEFI, fearing they will be penalized for “poor vaccination technique”. A mutual trusting relationship should be developed with supervisors so that health workers feel confident to report such events/incidents to their supervisors and the supervisors will support them in correcting any immunization error which might be contributing to the incidents.

Follow-up actions

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted. However, it must be accepted that in some cases the relationship to vaccine will never be clear.

Table 5: Provides a summary of actions that are usually taken when different types of AEFI occur:

Vaccine Reaction	If a higher reaction rate than expected from a specific vaccine or lot, then obtain information from the manufacturer and consult with WHO/UNICEF/MFDA/MTAGI to consider: ➢ Withheld or withdrawing that lot ➢ Quality control at Reference Lab ➢ Inform manufacturer about the decision ➢ Obtaining vaccine from a different manufacturer or different lot from the same manufacturer However, It is important to ensure the continuationof the NIP Programme, while assuring the vaccine safety
Immunization Error	Correcting cause of the error. This may mean one or more of the following: ➢ Change in logistics for supplying vaccine and other injection safety ➢ Change in procedures at the health facility items ➢ Training of field workers ➢ Intensified supportive supervision and follow-up Whatever action is taken, it is important to review at a later date to check that the programme 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 immunization- error related and, that the most likely explanation is a temporal association between the event and vaccine/vaccination. 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 ensure that the event was truly coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.
Immunization anxiety related Reaction/ ISRR	Assurance to the patients / parents and health (field) staff

Communication with Parents and Health Care Providers

The parents and the concerned immunization staff need to be kept informed about the results of investigation. In addition, the wider community and perhaps the entire country may need to be informed of the results of investigation and corrective action taken. It is important that not only the risks of immunization are communicated in such situations but the benefits of immunization as well.

Admit uncertainty, investigate fully, and keep the community informed. Avoid making a premature statement about the cause of the event before investigation is complete. If the cause is identified as a programme error, it is vital not to lay personal blame on anyone, but to focus on system-related problems that resulted in programme error(s) and steps being taken to correct the problem.

In communicating with the community, it is useful to develop links with community leaders and field workers so that information can be rapidly disseminated.

Key points to be considered when communicating with parents during or after an AEFI has occurred.

- Listen sympathetically to parents and their concerns
- Reassure and support the parent or patient
- Do not make false promises
- Help the parent/caregiver with taking the AEFI patient to hospital/health facility
- Keep the parent/guardian routinely informed of the progress of the patient

The field workers need to be supported and provided with appropriate information to respond directly to community concerns.

Communication with media

The mass media (newspaper, radio and television) play an important role in public's perception of vaccination and can have a positive or negative influence. The support of mass media for vaccination depends to a large extent on communication skills of the health authority. Statements and press conferences are useful tools to communicate with media when an adverse event occurs.

Media are most interested in stories that will attract attention and boost their sales/audience. If given inappropriate information, media can present the health service or officials responsible for immunization as being uncaring, impersonal, incompetent, or even dangerous.

Media can also be a helpful partner in communicating public health messages such as reminding public of the importance of immunization and the risks of the diseases. Building a personal relation with key health reporters will help them to understand the public health perspective.

The guiding principle for dealing with media must be honesty and building up trust. Trust and credibility are difficult to achieve; if lost, they are even more difficult to regain. It is vital to prepare before any media contact with:

- key messages
- Answers for likely and awkward questions
- Identifying which issues not to respond to (e.g. blaming an individual or guess on the cause before investigation is complete)

Messages need to be as simple as possible. Use simple words and short sentences. The key messages should be kept to a minimum and are likely to include some of these facts:

- benefit of immunization in preventing disease is well proven
- it is very risky not to immunize (risk of disease and complications)
- vaccine-preventable diseases caused millions of death and/or disability before introduction of vaccines, and that situation would return without continued use of vaccines
- vaccines do cause reactions, but these are rarely serious and hardly ever cause long-term problems (use Tables-1 and Table-2 to outline known risks of suspect vaccines)
- immunization safety is of paramount importance, and any suspicion of a problem is investigated (advantage of well established AEFI Surveillance System)
- the AEFI is currently being investigated, but is likely to be coincidental/due to a local problem (depending on type of event), and the immunization programme must continue to keep the population safe from disease
- action is being taken

It is essential to present information to the media in a way that will generate a sense of credibility and confidence by being:

- honest - never lie; if you do not know, say so, but promise to find out; note that a lie can become a bigger news story than the initial event
- caring - create a strong, compassionate, competent image of yourself and the service
- clear - avoid jargon; use simple phrases and give examples to clarify meaning
- serious - jokes can be disastrous and the subject is rarely amusing anyway
- aware of body language - it is of critical importance in perceptions
- responsible - don't be defensive, but accept responsibility appropriate to your position and avoid blaming someone else

- responsive - hold a daily press conference if it is needed; regular contact helps build a trusting relationship with media
- positive – re-frame the situation in positive terms; use terms such as vaccine safety (which has a positive connotation) rather than adverse event

When facing a hostile interviewer, prepare the following techniques:

- Block - respond to a negative question with a positive answer (e.g. when asked, "How many children have died from immunization?", answer: "Immunization saves lives. Since our immunization programme began X children have been immunized, and of them Y% might have died from one of these diseases. That is the context in which we must consider the tragic, but thankfully rare adverse events which follow immunization."
- bridge - having answered a difficult question, move quickly to something linked but positive
- Correct what is wrong - immediately correct information from the interviewer that is wrong. Be assertive, not aggressive and state the facts simply, factually and in a friendly way
- stay cool - no matter how bad it gets, don't get angry or defensive; stay friendly, polite and warm
- be assertive - means stating what you want to say in a clear way without getting aggressive; take time to think about the response and don't be rushed or forced

Bridge Technique

Question: Does vaccination cause abscesses?

Answer: (Face the element of truth) We know that vaccination can rarely cause abscesses. (here comes the first bridge….) That is why we train staff to avoid them by using sterile Auto Disable (AD) syringe for every child. (Now comes the second bridge) We also purchase only the highest quality vaccines approved by WHO and UNICEF. So we can assure parents/clients that we are providing quality immunization services.

Media usually appreciate an honest, polite, accurate and authoritative person who can provide them with information they need. Designating the spokesperson(s) to communicate with media limits the possibility of conflicting messages coming from different sources.

Who should be the Spokesperson?

It is important to assign a spokes person and the persons will be chosen after discussion with NIP and hospital management. The spokesperson should have adequate background knowledge of immunization and AEFI and have communication skills to engage with public and media.

Management of AEFI

Treatment must be the first response to an AEFI. Mild symptoms such as mild fever, pain are likely to be of short duration and can be managed by assuring and educating parents during immunization or treated by health workers. Health workers must also know how to identify serious AEFIs and when to refer.

Appendix: CASE DEFINITIONS AND MANAGEMENT OF AEFIs (with reference to Brighton collaboration)

Adverse event	Case definition	Treatment
Fever	The fever can be classified (based on rectal temperature) as: Mild fever: 38˚ C to 38.9˚C, High fever: 39˚ C to 40.4°C and Extreme fever (hyperpyrexia): higher than or equal to (≥ 40.5°C)	Symptomatic; paracetamol, tepid sponging
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial: Existence of infection (e.g. purulent, inflammatory signs, fever, and culture), Sterile abscess: There is no evidence of bacterial Infection following investigation.	Incise and drain; antibiotics if bacterial. Application of local ointment and hot compression is **NOT** recommended
Severe local reaction	Redness and/or swelling centred 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 or requires hospitalization. Local reactions of lesser intensity occur commonly and 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.
Mild Allergic Reaction	Mild allergic reactions may opresent with localized urticaria. These manifestations should be observed to see for extension and /or involvement of other systems.	Self-limiting; supportive care; anti-histamines
Anaphylaxis	Anaphylaxis is a severe allergic reactions with involvement of 2 or more organ system. Usually skin manifestation with other systemns	Inj Adrenalin

	include circulatory, respiratory involvement or gastrointestinal system.	
Arthralgia	Joint pain usually including the small peripheral joints. **Persistent** if joint pain lasting longer than 10 days, **transient:** if lasting up to approximately 10 days	Self-limiting; analgesics
Hypotonic hypo responsive episode (HHE or shock-collapse	Sudden onset of paleness or cyanosis – or failure to observe/ recall, decreased level or loss of responsiveness (hypo responsive), decreased level or los of muscle tone (hypotonic) occurring within 48 (usually less than 12) hours of vaccination.	The NIPsode is transient and self-limiting, no treatment is required. It is **not** a contraindication to further doses of the vaccine.
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated ≥39˚ C (rectal). Afebrile seizures: if temperature is normal	Self-limiting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants.
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed by positive blood culture. (if possible). Needs to be reported as possible indicator of programme error.	Critical to recognize and treat early. Urgent transfer to hospital for I.V antibiotics & fluids.
Thrombocytopaenia	Serum platelet count of less than 50,000/ml leading to bruising and/or bleeding	Hospitalized. Usually mild and self-limiting; occasionally may need steroid or platelets.
Persistent Screaming	Inconsolable continuous crying lasting at least 3 hours accompanied by high pitched screaming.	Self-limiting; supportive care;

Adverse event	**Case definition**	**Treatment**

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 programme error	Critical to recognize and treat early. Urgent transfer to hospital for intravenous antibiotics and fluids.
Encephalopathy/ Encephalitis	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; and distinct change in behaviour lasting one day or more. Cases occurring within 72 hours after vaccination should be reported.	No specific treatment available; supportive care.
Brachial neuritis	Dysfunction of nerves supplying the arm/shoulder with onset of deep steady, often severe aching pain in the shoulder and upper arm followed by weakness and wasting in arm/shoulder muscles. Sensory loss may be present, but is less prominent and may affect both arms.	Symptomatic only; analgesics.
Disseminated BCG infection	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of *Mycobacterium bovis* BCG strain. Usually in immuno-compromised individuals	Should be treated with anti-tuberculous regimens including isoniazid and rifampicin.
Lymphadenitis (includes suppurative lymphadenitis)	Either at least one lymph node enlarged to 1.5 cm in size (one adult finger width) or larger; a draining sinus over a lymph node. Almost exclusively caused by BCG and then 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 skin. If so, or already draining, surgical
Osteitis/ Osteomyelitis	Inflammation of the bone either due to BCG immunization (occurring within 8-16 months after immunization) with isolation of *Mycobacterium bovis* BCG strain or caused by other bacterial infection.	Should be treated with anti-tuberculous regimens including
Acute flaccid paralysis (Vaccine associated	Acute onset of flaccid paralysis within 4 to 30 days of receipt of oral poliovirus vaccine (OPV), or within 4 to 75 days after contact with a vaccine recipient and	No specific treatment available; supportive care.

paralytic poliomyelitis)	neurological deficits remaining 60 days after onset, or death.	
Anaphylaxis	Severe immediate (within 1 hour) allergic reaction with involvement of two or more systems. Usually with skin changes and leading circulatory failure with or without bronchospasm and or Laryngospasm / laryngeal oedema leading to respiratory distress.	Adrenaline injection (See Appendix- 6)

Anaphylaxis

Anaphylaxis is a severe allergic reaction to a foreign substance that occurs rapidly and may be fatal in some cases. Anaphylaxis is extremely rare. One of the most serious AEFIs that could

occure after vaccination is anaphylaxis. The estimated annual reported rate of anaphylaxis ranges from **0.4 to 1.8 reports per 1,000,000 doses** of vaccines distributed.

Prior to vaccination a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) should be sort. Vaccinators should have uptodate information specific vaccines they are administering (should be familiar with the information on the product insert). This includes information on vaccine handling, side effects, contraindications and precautions etc, this is especially important if giving new vaccines or optional vaccines.

Vaccines should be administered in settings where immediate allergic reactions, should they occur, can be appropriately managed. All vaccinators must be trained to recognize immediate vaccine reactions including anaphylaxis. Each vaccination center should have an SOP on the steps to follow in case of a serious AEFI following vaccination such as anaphylaxsis in the vaccination site.

All vaccinator must be familiar with contraindications and precautions for the vaccines they are administering. Prior to vaccination these information should be obtained as this will decrease the preventable AEFIs.

After any vaccination individuals should be monitored for at least 15 minutes and anyone with a past history suggestive risk of allergies should be monitored for 30 minutes.

In the case of an anaphylaxis following immunization, the vaccinator must follow the protocol given below including call for assistance and administration of the emergency treatment at the site of immunization.. Vaccination teams must carry an anaphylaxis response kit as. After immediate treatment there should be prior designated mechanism to transfer individuals to hospitals.

Common conditions that maybe mistaken for anaphylaxis

	ANAPHYLAXIS	VASOVAGAL	ANXIETY
DEFINITION	An acute systemic and potentially fatal allergic reaction to a foreign substance. IgE-mediated antibody induces histamine release from tissue mast cells.	A temporary unconsciousness caused by diminished blood supply to the brain due to painful stimuli or emotional reaction.	A protective physiological state recognized as fear, apprehension, or worry.
ONSET	Usually slower, most instances begin within 30 minutes after immunization.	Sudden, occurs before, during, or shortly after immunization; recovery occurs within one to two minutes	Sudden, occurs before, during, or shortly after immunization; recovery occurs within one to two minutes
SKIN	- warm, clammy and flushed - pruritus and urticaria (>90% of cases) - progressive, painless swelling (face, mouth and tongue)	- pale - excessive perspiration - cold, clammy	- pale - excessive perspiration - cold, clammy
BREATHING	- sneezing, coughing, wheezing, labored breathing - upper airway swelling (hoarseness and/or difficulty swallowing) possibly causing airway obstruction	- normal or shallow, irregular, labored	- rapid and shallow (hyperventilation)
PULSE	- rapid, weak, irregular	- slow, steady	- rapid
BLOOD PRESSURE	- hypotension which may progress to shock and collapse	- decreased systolic and diastolic	- normal or elevated systolic
SYMPTOMS and BEHAVIOURS	- uneasiness, restlessness, agitation - not all signs/symptoms will be exhibited in each person; usually one body system predominates.	- fearfulness - light-headedness - dizziness - numbness, weakness - sometimes accompanied by brief clonic seizure activity	- fearfulness - light-headedness, dizziness - numbness, weakness - tingling around lips and spasm in the hands and feet - hyperventilation
GASTRO-INTESTINAL	- nausea and vomiting - abdominal pain, diarrhea	- nausea	- nausea
OTHER SYMPTOMS	- loss of consciousness - progression of injection site reaction beyond hives and swelling	- Loss of consciousness is possible; of short duration (one to two minutes)	- loss of consciousness in severe cases; of short duration

Other conditions that maybe mistaken for anaphylaxis

Diagnosis	Onset: symptoms and signs
Hypotonic hyporesponsive episode	Onset 2-6 hours post immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, respiratory or cardiovascular compromise
Seizure	Onset atleast 6-8 hours post vaccination with a killed vaccine. Sudden unresponsiveness usually with tonic clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromis unless apnea or aspiration

Aspiration of oral vaccine (example OPV or rotaviral vaccine)	Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infants. No skin rash or cardiovascular compromise.
Severe coincidental disease	Usually due to coincidental- unrecognized congenital heart disease or occult infections. May have respiratory or cardiovascular compromise but there are usually symptoms, signs or investigations to indicate alternate cause
Immunization-error related	Immediate toxic drug reaction with symptoms and signs due to drug toxicity, Reported with immunization-error related which have resulted from inadvertent administration oif a muscle relaxant or insulin.

STEPS IN MANAGEMENT OF ANAPHYLAXIS

Emergency treatment of anaphylaxis

1. Assess situation: Is it anaphylaxis Assess (ABCDE) Airway, breathing, circulation, disability and exposure

a) To assess adequately the nature of any post-immunization reaction that could be of an anaphylactic nature, it is important to assess comprehensively the various organ systems that may be implicated. In anaphylaxis 2 or more systems are affected and usually presents with skin rash.

I. Cardiac:
- Level of consciousness (impairment might reflect hypoxia)
- Pulse rate (assess for rapid, weak, irregular pulse).
- Pallor or cyanosis around perioral area
- Capillary refill time (if a compromise in perfusion is suspected)
- Blood pressure, if required equipment is available

II. Respiratory:
- Hoarse cry/voice, stridor (a high-pitched noisy sound occurring during inhalation), cough, wheezing, shortness of breath or labored breathing, use of accessory muscles, etc.
- Respiratory rate

III. Cutaneous:
- Injection site(s) redness, swelling or hives Facial flushing, itching, hives or welts and their extent, angioedema, other rashes.In general, the

sooner the onset, the more rapidly evolving and severe the anaphylactic reaction

IV. Gastrointestinal system:
- Nausea, vomiting, diarrhea, abdominal pain
- In general, the sooner the onset, the more rapidly evolving and severe the anaphylactic reaction.

2. Call for help. Do not leave the client under any circumstances
3. Position the client in the recumbent position (lay flat on back) and elevate legs, as tolerated symptomatically. If breathing difficulty elevate head and chest slightly as tolerated. This slows progression of circulatory compromise, if present, by preventing orthostatic hypotension and helping to divert effective circulation from the periphery to the head, heart and kidneys. If unconscious or vomiting keep in recovery position or on one side.
4. Administer adrenalin (1:1,000) IM into an unimmunized limb immediately. DO NOT GIVE ADRENALIN TO THE LIMB USED FOR IMMUNIZATION. The most important step in the management of anaphylaxis is the immediate administration of aqueous adrenalin1:1,000. Failure to use adrenalin promptly is more dangerous than its improper use. There is no contraindication to adrenalin administration in anaphylaxis
5. DO NOT inject adrenalin into the same muscle mass (e.g., thigh) as the vaccine was administered (this may increase blood flow locally, thereby increasing absorption of the agent)If both thighs were used for immunization.
6. Give adrenalin IM into deltoid if client is > 12 months old
7. Give adrenalin SC into upper outer triceps area of the arm(s) if the client is < 12 months old.
8. Injection of adrenalin can be made through clothing, if necessary.
9. Repeat dosing of adrenalin.
    - If major symptoms (i.e, breathing difficulties, level of consciousness.) Do not improve or worsen after the first dose, additional doses of adrenalin are warranted. Repeat adrenalin twice at five-minute intervals, as needed (maximum: three doses).
10. Alternate right and left thigh or arm sites for repeat doses of adrenalin (to maximize absorption of adrenalin). DO NOT give in the limb used for vaccination.
11. Monitor the patient closely until EMS arrives. Perform cardiopulmonary resuscitation (CPR), if necessary, and maintain airway. Keep patient in recumbent position (flat on back) unless he or she is having breathing difficulty. If breathing is difficult, patient's head may be elevated, provided blood pressure is adequate to prevent loss of consciousness. If blood pressure is low, elevate legs. Monitor blood pressure and pulse every 5 minutes.
12. Record the patient's reaction (e.g., hives, anaphylaxis) to the vaccine, all vital signs, medications administered to the patient, including the time, dosage, response, and the name of the medical personnel who administered the medication, and other relevant clinical information. 6 Notify the patient's primary care physician.
13. 20% of anaphylaxis episodes follow a biphasic course with recurrence of the reaction after a two-to nine-hour asymptomatic period, hospitalization or a long period of observation is recommended for monitoring.

Management of anaphylaxis

Anaphylactic reaction?

Asses Airway, Breathing, Circulation, Disability and Exposure (ABCDE)

Diagnosis – Look for:
- Acute onset of illness
- Life threatening Airway and/ or breathing and or Circulation problems
- And usually with skin changes

- Call for help
- Lie patient flat
- Raise patient's legs

ASSESSMENT

In anaphylaxis 2 or more systems are affected and usually presents with skin rash.

System	Sign and symptoms
Cutaneous	• Injection site(s) redness, swelling or hives Facial flushing, itching, hives or welts and their extent, angioedema, other rashes.In general, the sooner the onset, the more rapidly evolving and severe the anaphylactic reaction
Respiratory	• Hoarse cry/voice, stridor (a high-pitched noisy sound occurring during inhalation), cough, wheezing, shortness of breath or labored breathing, use of accessory muscles, etc. • Respiratory rate
Cardiac	• Pulse rate (assess for rapid, weak, irregular pulse). • Pallor or cyanosis around perioral area • Capillary refill time (if a compromise in perfusion is suspected) • Blood pressure, if required equipment is available • Level of consciousness (impairment might reflect hypoxia)
Gastrointest-inal system	• Nausea, vomiting, diarrhea, abdominal pain • In general, the sooner the onset, the more rapidly evolving and severe the anaphylactic reaction.

Administer UNDILUTED Injection Adrenaline (1:1000) through deep intramuscular route to mid third of anterolateral thigh
- **0.01ml/kg for age <6 months (max 0.15ml)**
- **0.15ml for age 6months - 6 years**
- **0.3ml for age 6 years - 12 years**
- **0.5ml for age > 12 years of age and adults**
- Repeat dose of adrenalin maybe given at 5 minute intervals at different sites (for maximum 3 doses if symptoms does not improve) and further doses if required maybe given in hospital setting (do not give adrenalin to the limb used for vaccination)
- **CPR should be initiated at any point if necessary**
- **MONITOR VITALS AND TRANSFER TO NEAREST EMERGENCY CARE**

AS SOON AS SKILLS AND EQUIPTMENT AVAILABLE
- Establish airway and give high flow oxygen
- Administer IV fluid (Normal saline or Ringer lactate) to maintain blood pressure 20ml/kg in children, 500-1000ml in adults.
- Administer Injection Pheniramine Maleate (Inj Avil 45.5mg/ 2ml), children IM only~ 0.3mg/kg/dose
  0.5-0.7ml age 1-2 years (~11-14 kg body weight)
  0.8-1.3ml age 3-5 years (about 20 kg body weight)
  1.0 -1.5ml aged 6-11 years (up to about 25 kg body weight)
  1.0-2ml age ≥12 years and adults
- Administer Injection Hydrocortisone IM or slow IV
  25mg age < 6 months
  50mg age 6 months to 6 years
  100mg age 6-12 years
  200 mg >12 years of age and adults
- Monitor and maintain vitals: Heart rate, respiratory rate, blood pressure, pulse oximetry and ECG

The normal respiratory rate varies by age (approximate):
- <1 year 30-40 min
- >1 to 2 years 26-34 min
- >2 to 5 years 24-30 min
- >5 to 12 years 20-24 min
- **>12 years 12-20 min**

Normal heart rate by age (approximate)
- Newborn to 3 months 140 min
- >3 months to 2 years 130 min
- >2 to 10 years 80 min
- >10 years 75 min
- **Adults 60-100 min**

Lower Limit of SBP by Age
- 0 to 1 month 50-60 mmHg
- >1 to 12 months 70 mmHg
- >1 to 10 years 70 + (age in years x 2) mmHg
- >10 years 90 mmHg
- **Adults: aim to keep at usual BP or if not known aim for >100 mmHg**

Table 1: Frequency of occurrence of signs and symptoms of anaphylaxis	
Signs and symptoms	**Approximate frequency**
Cutaneous	**90%**
Generalized urticaria (hives)and/or angioedema (welts)	85 – 90%
Flushing	45 – 55%
Pruritus (itchiness) with or without rash	2 – 5%
Respiratory	**40 – 60 %**
Upper airway angioedema (stridor)	50 – 60%
Dyspnea (difficulty breathing), wheeze	45 – 50%
Rhinitis (nasal congestion)	15 – 20%
Dizziness, syncope (fainting), hypotension	**30 – 35%**
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25 – 30%
Miscellaneous	
Headache	5 – 8%
Substernal (chest) pain	4 – 6%
Seizure	1- 2%
From: The diagnosis and management of anaphylaxis: an updated parameter. (2005). Journal of Allergy and Clinical Immunology, 115, S483-523.	

TABLE 1 CRITERIA FOR MEETING BRIGHTON CASE DEFINITION OF ANAPHYLAXIS

1. COURSE OF ILLNESS: must be able to check both 1.1 AND 1.2 to meet any level of certainty for anaphylaxis	
☐ **1.1 SUDDEN ONSET of signs & symptoms** *Working group defines this as "an event that occurred unexpectedly and without warning leading to a marked change in a subject's previously stable condition"*	☐ **1.2 RAPID PROGRESSION of signs & symptoms** *Working group did not define this and further noted that "Using an arbitrarily restrictive setpoint might bias future data collection unnecessarily." Accordingly, it is open to judgement.*

2. ≥ 2 body systems involved: check all symptoms/signs present by checking appropriate boxes in rows below. Ideally these should be documented in writing (E.G. AEFI report, clinical record in immunization clinic, Emergency room, or other clinical setting. Alternatively, a verbal report from a professional (R.N., M.D, Pharmacist) who witnessed the event.			
Body System	**B. MAJOR CRITERIA**	**C. MINOR CRITERIA**	
SKIN **excluding hereditary angioedema*	☐ Generalized urticaria (hives) ☐ Generalized erythema ☐ Angioedema* (general or localized including lip) ☐ Generalized pruritus WITH skin rash	☐ Localized injection site urticaria ☐ Red AND itchy eyes ☐ Generalized prickle sensation ☐ Generalized pruritus WITHOUT skin rash	
RESPIRATORY (RESP)	☐ Bilateral wheeze (bronchospasm; by stethoscope) ☐ Stridor ☐ Upper airway swelling (tongue, throat, uvula, larynx) ☐ ≥ 2 indicators of respiratory distress: ○ Tachypnea ○ Cyanosis ○ Grunting ○ Chest wall retractions ○ Increased use of accessory respiratory muscles	☐ Persistent dry cough ☐ Hoarse voice ☐ Sensation of throat closure ☐ Sneezing OR rhinorrhea ☐ Difficulty breathing WITHOUT wheeze or stridor	
CARDIO-VASCULAR (CV)	☐ Measured hypotension ☐ ≥ 3 signs of uncompensated shock: ○ Tachycardia ○ Capillary refill >3 seconds ○ Reduced central pulse volume ○ Decreased level or loss of consciousness	☐ ≥ 2 signs of reduced peripheral circulation ○ Tachycardia ○ Capillary refill >3 seconds ○ Decreased level of consciousness	
GASTRO-INTESTINAL (GI)	NONE	☐ Nausea ☐ Abdominal pain	☐ Vomiting ☐ Diarrhea
LABORATORY	NONE	☐ Elevated mast cell tryptase (> upper normal limit for laboratory doing test)	

TABLE 3 LOGIC TO DETERMINE LEVEL OF DIAGNOSTIC CERTAINTY

Level of Certainty	Logic to reach level of certainty for Anaphylaxis
Level 1, 2 & 3	**Must meet both of the following criteria (if one or both not met, it is not a case – level 5):** ___Sudden onset of symptoms/signs ___Rapid progression of symptoms/signs
Use the pattern of MAJOR and minor criteria met for skin, respiratory, cardiac and gastrointestinal (GI) systems and laboratory result from the table above to determine the highest level of diagnostic certainty (with level 1 > level 2 > level 3).	
Level 1	≥1 Skin MAJOR AND [≥ 1 Respiratory MAJOR AND / OR ≥ 1 Cardiac MAJOR]
Level 2 *NOTE: 4 different ways to meet level 2*	1. ≥ 1 Skin MAJOR AND [≥ 1 Respiratory minor AND / OR ≥ 1 Cardiac minor]
	2. ≥ 1 Respiratory MAJOR AND ≥ 1 Cardiac MAJOR
	3. ≥ 1 Respiratory MAJOR AND ≥ 1 minor from a different system (Skin, Cardiac, GI, lab)
	4. ≥ 1 Cardiac MAJOR AND ≥ 1 minor from a different system (Skin, Respiratory, GI, lab)
Level 3 *NOTE: 2 different ways to meet level 3*	1. ≥ 1 Respiratory minor AND ≥ 1 minor from each of 2 different systems (Skin, Cardiac, GI, lab)
	2. ≥ 1 Cardiac minor AND ≥ 1 minor from each of 2 different system (Skin, Respiratory, GI, lab)
Level 4	Reported anaphylaxis with insufficient evidence to meet any of levels of diagnostic certainty
Level 5	**Not a case of anaphylaxis:** if unable to check 1.1 and 1.2 (i.e., onset not sudden and did not progress rapidly)

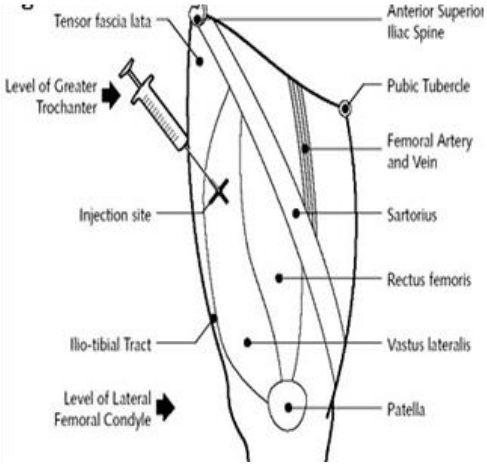
Anaphylaxis response kit contents

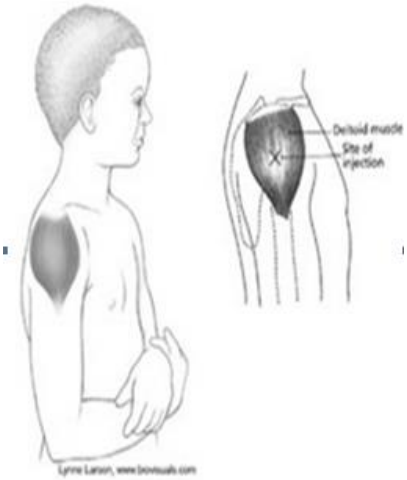
- Copy of anaphylaxis management protocol.
- At least 3 ampoules of adrenalin 1mg/mL
- 1 mL syringes x 4
- Needles (25 to 27 gauge)1 inch - 1½ inch
- Alcohol swabs

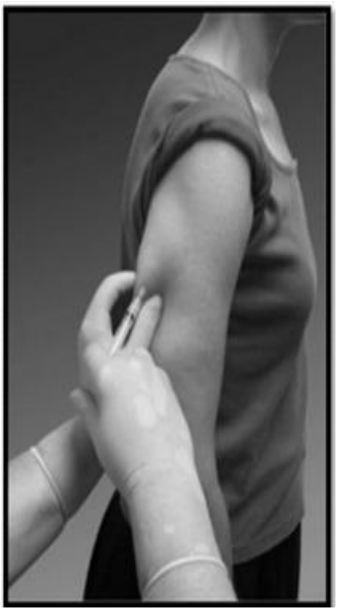
At all vaccination sites: it is recommended to have facility for assessing blood pressure, pulse rate, respiratory rate and capillary refill time (a timing device to check rates should be made available). Either automated or manual blood pressure monitor, with appropriate cuff sizes is acceptable. There should be access to emergency medical support if required such as resuscitation or support for transportation if required. Prior to any vaccination, protocol for medical emergency should be defined. All vaccination sites should be linked to an anaphylaxis management centre (emergency department of health care facility), where cases requiring further treatment or observation should be referred.

Injection Location Considerations

- The correct site of intramuscular (IM) administration of adrenalin is ALWAYS the vastus lateralis located at the middle third of the lateral thigh [See image 1].
- In case of arms deltoid region of both arms could be used.
- In case of thighs IM anterolateral thigh could be used if both thighs are used in vaccination
- In children >12 months of age IM deltoid region could be used.
- In infants SQ upper outer triceps area is used.
- Do not give injection adrenalin to the same limb where vaccination has been given







Outer Middle third of thigh (IM)

Deltoid area (IM)

Outer tricep area (SC)

Causality Assessment

Causality assessment is the systematic review of data about an AEFI case; it aims to determine the likelihood of a causal association between the event and the vaccine(s) received.

The quality of the causality assessment depends upon:

- the performance of the AEFI reporting system in terms of responsiveness, effectiveness and quality of investigation and reports;
- the availability of adequate medical and laboratory services and access to background information;
- the quality of the causality review processes

A cluster of similar adverse events is likely to arise from immunization errors or vaccines. It is therefore important to identify if control/ un-vaccinated people also developed similar symptoms around the same time.

Investigation of a cluster requires:

- Establishment of a case definition, if there is no case definition laid down previously
- Identification of all vaccinated population who meet the case definition
- Obtaining immunization histories (when, where and which vaccines were given)
- Identifying any common exposures among the cases

Steps of Causality Assessment

All members of the investigation team should sit together and critically review all available information and come to a best possible conclusion of the findings and make appropriate recommendations.

Until investigation is complete, a "working hypothesis" is all that can be formulated. Later it will be possible to analyze data, making a final diagnosis and identifying the cause. Causes of AEFI are classified in five ways: Immunization error, Vaccine product related reaction, Vaccine quality defect –related reaction, Immunization anxiety-related reaction and Coincidental,

Causality assessment has four steps, as follows:

• Step 1: **Eligibility**. The first step aims to determine if the AEFI case satisfies the minimum

criteria for causality assessment as outlined below.

• Step 2: **Checklist**. The second step involves systematically reviewing the relevant and

available information to address possible causal aspects of the AEFI.

• Step 3: **Algorithm**. The third step obtains a trend as to the causality with the information

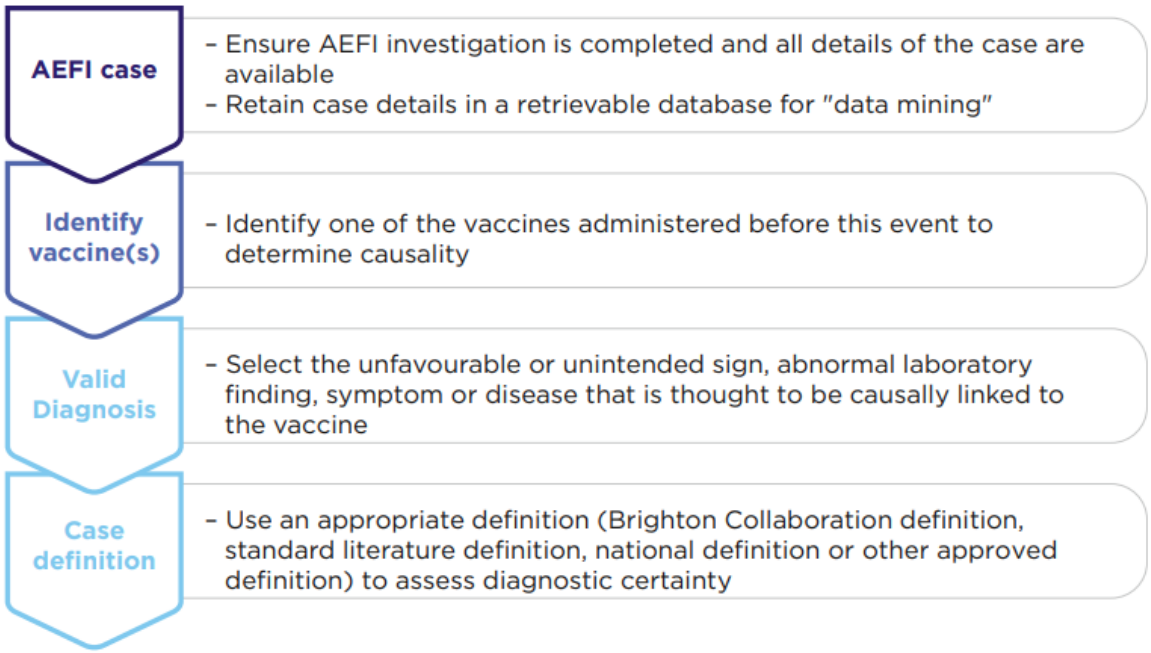
gathered in the checklist.

• Step 4: **Classification**. The fourth step categorizes the AEFI's association to the vaccine or vaccination on the basis of the trend determined in the algorithm

ELIGIBILITY

Before proceeding with causality assessment, it is necessary first to confirm that the vaccine was administered before the event occurred. This can be ascertained by eliciting from the relevant informants a very detailed and careful history and physical findings. It is also essential to have a

Fig. 1. Causality assessment – Eligibility



valid diagnosis for the reported AEFI, which could be an unfavorable or unintended sign, an abnormal laboratory finding, a symptom or a disease.

The valid diagnosis should meet a standard case definition (or it could also be a syndromic case definition). If available, it is best to adopt the Brighton Collaboration case definition.

At this stage it is also essential for the reviewers to define the "causality question"

Create your question on causality here

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

It is important that, if an AEFI is reported and does not meet the eligibility criteria, attempts should be made to collect additional information to ensure that the criteria are met. All cases reported (including ineligible cases) should be stored in a repository (preferably electronic) so that they can be accessed when additional information becomes available through reports of similar cases or through periodic data mining. At this point of the assessment, the assessor has to make a decision if the information that is available at hand is sufficient to proceed.

CHECKLIST

	Y	N	UK	NA	REMARKS
Is there a strong evidence for other cause?					

1. In this patient does the medical history, clinical examination and/or investigations, confirm another cause for the event?					
II. Is there a known causal association with the vaccine or vaccination?					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?					
2. Is there a biological plausibility that this vaccine could cause such an event?					
3. In this patient, did a specific test demonstrate the causal role of the vaccine?					
Vaccine quality					
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?					
Immunization error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?					
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?					
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?					
8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?					
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?					
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?					
Immunization anxiety (Immunization stress related responses - ISRR)					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc)?					

II (time): Was the event in section II within the time window of increased risk (i.e. 'Yes" response to questions from II 1 to II 11 above)					
12. In this patient, did the event occur within a plausible time window after vaccine administration?					
III. Is there strong evidence against a causal association?					
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) against a causal association between the vaccine and the event?					
IV. Other qualifying factors for classification					
1. In this patient, did such an event occur in the past after administration of a similar vaccine?					
2. In this patient, did such an event occur in the past independent of vaccination?					
3. Patient without vaccination (background rate)?					
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?					
5. Was this patient taking any medication prior to the vaccination?					
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?					

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

The checklist is designed to assemble information on the patient-immunization-AEFI relationship in the following key areas:

- evidence for other causes;
- association of the event and the vaccine/vaccination with the vaccine product(s), immunization error or immunization anxiety (if there is an association, it is also important to find out if the event occurred within a plausible time window);
- evidence against a causal association;
- other qualifying factors for classification such as previous history of a similar event, the background rate of the event, pre-existing, present and past health conditions, potential risk factors, other medications, exposure to triggering factors etc.

Immunization Error

Immunization errors are the most commonly reported adverse events. These occur as a result of inappropriate storage, transportation, reconstitution, preparation and administration of vaccines. It is extremely important that these AEFIs are reported and addressed for early correction.

An immunization error 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.

If the cause of an AEFI is not initially clear, evidence of the following errors may help in identification and due attention during the causality assessment for each of following is useful and necessary.

- Too much vaccine given in one dose
- Immunization given in wrong place
- Wrong injection technique
- Syringes are contaminated
- Vaccine or diluents contaminated
- Vaccine reconstituted with incorrect diluents (count remaining unopened vials of vaccine and check whether there is matching quantity of the diluents from the same manufacturer)
- Separate syringes not used for each vial of freeze dried vaccine for reconstitution
- Wrong amount of diluents used
- Drugs substituted for vaccine or diluents
- Vaccine and diluent stored incorrectly
- Vaccine or diluents was expired (check expiry date of same batch number)
- Contraindications ignored, e.g. when a child who has had a severe reaction after a previous dose of DPT is immunized with the same vaccine
- Reconstituted vaccines kept for more than 6 hours; not discarded at the end of an immunization session and used at a subsequent one
- Used liquid vaccine vial is not discarded at the end of an immunization session and used at a subsequent one. (However, this is not applicable for fixed sites, where vaccine store facility is available and MDVP is practiced)

If programme error can be ruled out as the cause of AEFI under investigation, the investigation team should look for evidence that it was vaccine reaction or coincidental.

Vaccine Product Related Or Quality defects

Vaccine product related are events caused or precipitated by the vaccine when given correctly due to the inherent properties of the vaccine. These are vaccine components e.g., aluminum adjuvant, stabilizers and preservatives, antibiotics. Minor events settle without much interference with treatment and have no long-term consequences. Although serious events are very rare, it is important to investigate each case where the quality of vaccine is suspected. Vaccine quality defects : now very rare due to introduction of Good Manufacturing Practices (GMP), the vaccine manufacturers have started following GMP and strengthening of National Regulatory Authorities (NRAs)

The factors to be considered during causality assessment of such cases;

- Frequency of occurrence; whether the events occurred within the expected frequency range.

- Known reaction of the vaccine or not
- Event caused suspected due to the biological properties of the vaccine
- Significant temporal relationship for the event and the vaccine administration
- Past history of similar events; related or independently of vaccination
- Laboratory results helping the investigation

Immunization anxiety related Reaction

The types of reactions caused by immunization anxiety are

1. Vasovagal mediated reactions
2. Hyperventilation mediated reactions
3. Stress-related psychiatric disorders

The immunization anxiety reactions include fainting, light-headedness, dizziness, tingling around the mouth and in the hands; occasionally breathe holding in younger children may lead to unconsciousness.

Coincidental Events

When a medical event occurs after vaccination, it is usually believed that the event occurred due to vaccination. In fact, this event is AEFIs can result from underlying or emerging conditions of the vaccine as well as external exposures that can cause harm independent of immunization. These include:

1. Underlying or emerging condition(s) in the vaccinee which are manifested after vaccination
   a) Manifestation or complication of a congenital or inherited underlying disease condition
2. Conditions caused by exposure to something other than vaccine:
3. Infection due to agents such as bacteria, viruses, fungi or parasites.
4. Adverse reaction due to recent or concomitant medication or use of illicit substances.
5. Allergic and other hypersensitivity reactions due to exposure to allergens other than those present in the vaccine.

Identifying cause of a cluster:

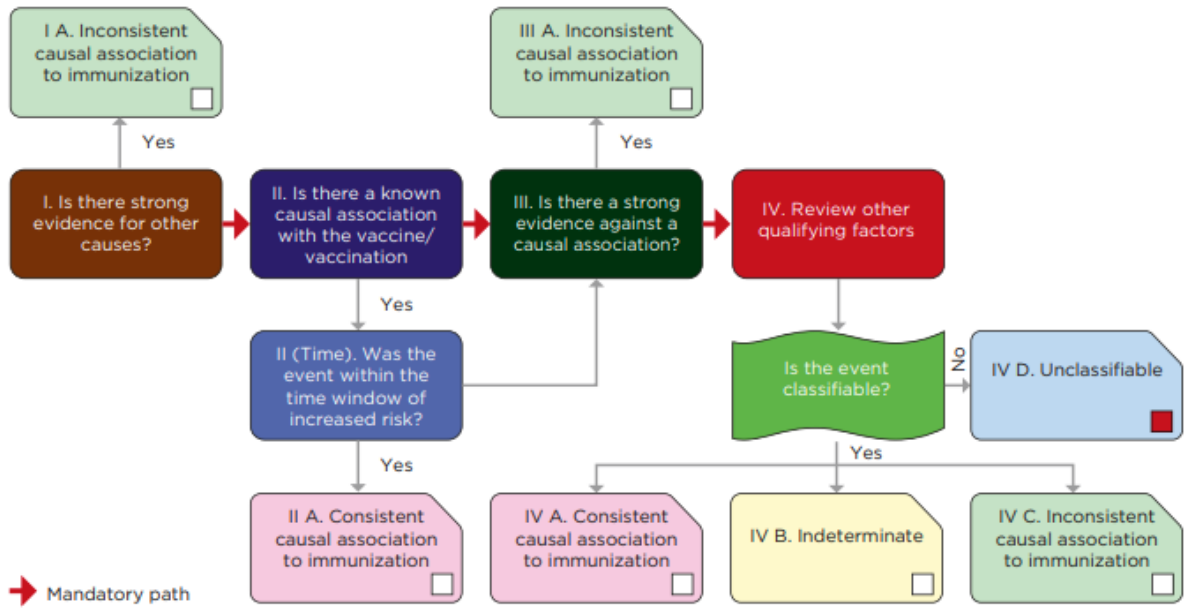
If all cases received vaccines from the same health worker/facility and there are no other cases from other health worker/facility, immunization error is more likely, but still possibility of vaccine reaction or coincidence or immunization anxiety reaction cannot be ruled out. If all cases received the same vaccine or lot from more than one facility, and there are no similar cases in the community, a problem with the vaccine is more likely, again immunization error or coincidence cannot be ruled out. If the event is a known vaccine reaction but occurring at an increased rate, an immunization error or a vaccine reaction are likely causes.

ALOGARITHM

After the checklist is completed, data related to the association under investigation is ready to be applied to the algorithm. The algorithm aims to be a roadmap for the decision-making of the reviewers. 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 unclassifiable

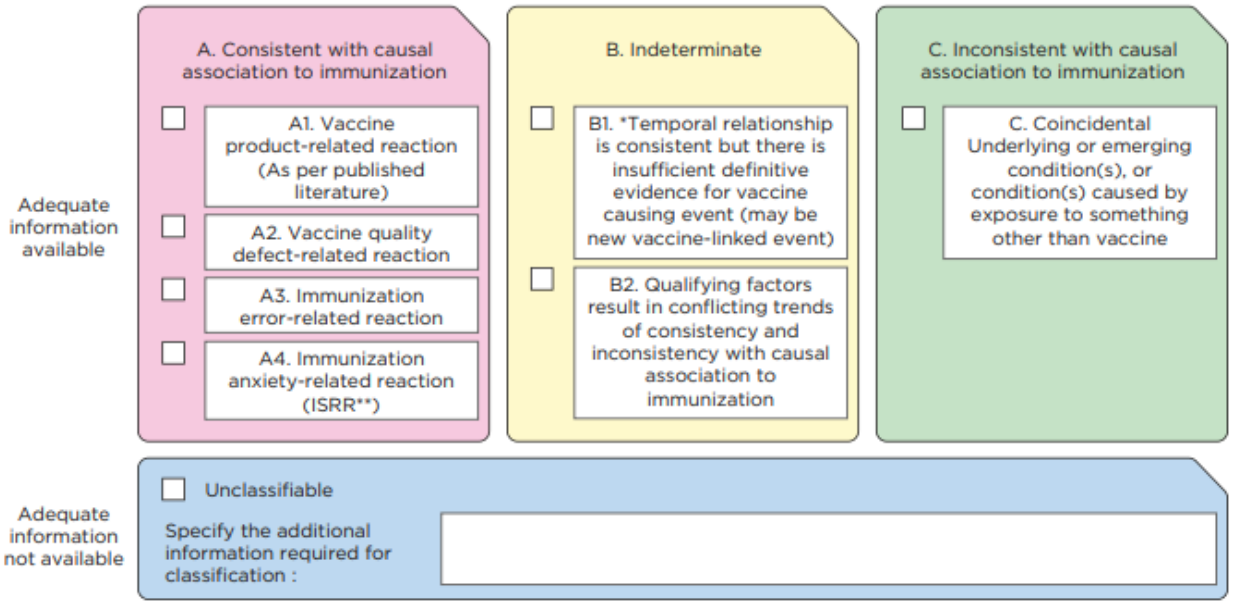
The algorithm allows the reviewers to focus logically and document their observations to the appropriate conclusions. "Yes" responses in the checklist should have corresponding conclusions in the algorithm. The boxes on the mandatory path (red arrow) correspond to the four major sections in the checklist (I to IV). It is essential that the reviewers evaluate all four boxes using the responses in the checklist. The conclusions are color-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.

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



CLASSIFICATION

The final classification is based on the availability of adequate information



*B1 : Potential signal and maybe considered for investigation
** Immunization stress related response

I. Case with adequate information for causality conclusion

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

A. Consistent causal association to immunization

- A1. Vaccine product-related reaction; or
- A2. Vaccine quality defect-related reaction; or
- A3. Immunization error-related reaction; or
- A4. Immunization anxiety-related reaction/Immunization stress related response (ISRR).

B. Indeterminate

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

C. Inconsistent causal association to immunization (coincidental)

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

II. Case without adequate information for causality conclusion

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

Submission of the AEFI Investigation Report

After completing investigation, the AEFI investigation team will submit report to respective National Immunization Programme Manager. The report includes filled in investigation form together with all medical records e.g. prescription, treatment sheet (if hospitalized), laboratory reports (if any), autopsy report (in case of death) etc. A copy of the AEFI report form should be attached with the investigation report. The programme will analyze the reports with the AEFI committee send the feedback to respective Clinical focal point who will inform the person.

National AEFI Committee

The National AEFI Committee will review the investigation reports of serious AEFI reported. The committee will play a critical role in confirming the causality assessments of selected investigations and in determining causality when not established with confidence by the investigation team. This committee will also evaluate, analyze and make recommendations of actions to be taken, support NIP programme in encouraging AEFI reporting and advice Programme Manager-NIP, Maldives Food and Drug Authority (MFDA), National Health Laboratory (NHL) at times of crisis and also regularly.

Resources

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https://brightoncollaboration.us/category/pubs-tools/case-definitions/companion-guides/

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Appendices

Appendix 1. Case Reporting Form

FORM 1

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

Patient Name:	***Reporter's Name:***
Patient's full Address:	Institution:
NIC/PPN: Telephone: Sex: ☐ M ☐ F	Designation & Department: Address:
***Date of birth:** _ _/_ _/_ _*	Telephone & E-mail:
Age at onset: _ _ *Years* _ _ *Months* _ _ *Days*	Date of reporting (by patient): _ _/_ _/_ _
Age category at onset: ☐ 5 to 18years ☐ 18 to 65 yrs ☐ More than 65 years	Date of report (by reporter): _ _/_ _/_ _

Health facility (place or vaccination centre) name & address:

Vaccine						Diluent (if applicable)			
*Name of vaccine	*Date of vaccination	*Time of vaccination	Dose (1st, 2nd, etc.)	*Batch /Lot number	Expiry date	Name of diluent	*Batch /Lot number	Expiry date	Date and time of reconstitution

***Adverse event(s):**

☐ Severe local reaction ☐ >3 dys ☐ beyond nearest joint
☐ Seizures ☐ febrile ☐ afebrile

☐ Vasovagal syncope
☐ Anaphylaxis
☐ Fever ≥38°C
☐ Abscess
☐ Sepsis
☐ Brachial Neuritis
☐ Encephalopathy
☐ Toxic shock syndrome
☐ Thrombocytopenia
☐ Guillain-Barre Syndrome
☐ Bell's Palsy
☐ Other (specify).....

Date AEFI started (Date of first symptom): _ _/_ _/_ _
Time: __ __: __ __

Describe AEFI (Signs & Symptoms):

Main Complaints:

Examination:

•GCS:	•Lungs:
•Pulse Rate:	•CVS:
•BP:	•P/A:
•Temperature:	•CNS:
•RR:	•Local Examination:
•SpO2	
•GRBS:	
•Capillary refill time: *(time taken for skin to come back to normal color after pressing fingertip for 5 seconds)*	

Diagnosis:

Treatment Given: **Admitted:** (Y / N) **Discharged:** (Y / N)

Discharge Advice:

Serious: Yes / No; ➔ **If Yes,** ☐ Death ☐ Life threatening ☐ Persistent or significant disability ☐ Hospitalization ☐ Congenital anomaly

Outcome: ☐ Observed for …. (mins) after vaccination ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died, If Died, date of death: _ _/_ _/_ _ Autopsy done: ☐ Yes ☐ No ☐ Unknown

Past medical history (including history of similar reaction or other allergies), concomitant medication and other relevant information (e.g., other cases). *Use additional sheets if needed:* ☐ Pregnant, if yes, Gestation: ☐ Lactating

First Decision making level to complete:

Investigation needed: ☐ Yes ☐ No If Yes, date investigation planned: _ _/_ _/_ _

National level to complete:

Date report received at National Level: _ _/_ _/_ _	AEFI worldwide unique ID:
Comments:	

Compulsory field* **Version: May 2021

FORM 2

Appendix 2: Case Investigating Form

National Immunization Program

Adverse Events Following COVID-19 Vaccination-Investigation Form

(only for Serious Events Following Immunization -Death/Disability/Hospitalization/Cluster)

SECTION A Basic Details

Atoll and Island: Case ID:

Place of vaccination (P): ☐ Gov. Health Facility ☐ Private Health Facility ☐ Other _____
Vaccination in (P): ☐ Campaign ☐ Routine ☐ Other (Specify): _____

Address of Vaccination Site:

Name of Reporting Officer: Date of Investigation: _ _ /_ _ /_ _
Designation/Position: Date of filling this form: _ _ /_ _ /_ _
Phone Number: This report is ☐ First ☐ interim ☐ Final
Email Address:

Patient Name:
(use a separate form for each case in a cluster)
Date of Birth (DD/MM/YY): _ _ /_ _ /_ _
OR Age at onset: _ _ *years* _ _ *months* _ _ *days*
OR Age group: ☐ *< 1year* ☐ *1-5 years* ☐ *> 5 years-18 years* ☐ *>18years- 60 years* ☐ *> 60 years*
Patients full address with landmarks (street name, house name, locality, phone number etc.):

Brand name of vaccines (including manufacturer / diluent received by the patient)	**Date of vaccination**	**Time of vaccination**	**Dose (e.g.: 1st, 2nd 3rd)**	**Batch number**	**Expiry date**
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent
				Vaccine	Vaccine
				Diluent	Diluent

Type of site (P): ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first key symptom *(DD/MM/YY):* _ _ /_ _ /_ _ _ _ Time of first symptoms *(hh/mm):* _ _ /_ _
Date of hospitalization *(DD/MM/YY):* _ _ /_ _ /_ _ _ _
Date first reported to health facility *(DD/MM/YY)*: _ _ /_ _ /_ _ _ _

Status on the date of investigation (P): ☐Died ☐Disabled ☐Recovering ☐Recovered Completely ☐ Unknown

If died, date and time of death *(DD/MM/YY):* _ _ /_ _ /_ _ _ _ (*hh/mm):* _ _ /_ _
Autopsy done?(P): ☐Yes (date): _____ No, Planned on (date): _____Time: _____
Attach report (if available)

SECTION B- Relevant Patient Information Prior to Immunization		
Criteria	**Finding**	**Remarks (if yes Provide details)**
Past history of similar event?	Yes/No/Unkn	
Adverse event after any previous vaccinations?	Yes/No/Unkn	
History of allergy to vaccine, drug or food?	Yes/No/Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes/No/Unkn	
Pre-existing acute illness (30days) prior to vaccination?	Yes/No/Unkn	
Has the patient tested positive COVID19 prior to vaccination?	Yes/No/Unkn	
History of hospitalization in last 30 days, with cause?	Yes/No/Unkn	
Was the patient receiving any concomitant medication? (if yes, name the drug, indication, doses and treatment dates)	Yes/No/Unkn	
Family history of any disease (relative to AEFI) or allergy?	Yes/No/Unkn	
For adult women • Currently pregnant? Yes (Weeks) _____ / No / Unknown • Currently Breast feeding? Yes/No		
For infants The birth was ☐ full term ☐pre-term ☐ Post-term Birth weight: _____ Delivery procedure was ☐ Normal ☐Cesarian ☐Assisted (forced, vacuumed etc.) ☐with complications specify		

SECTION C- Details of First Examination** of Serious AEFI case		
Source of information (Pall that apply): ☐Examination by the investigator ☐Documents ☐Verbal autopsy other _____ *if from verbal autopsy, please mention the source* _____		
Name of the person who first exmined/ treated the patient: Name of the person treating the patient: Other sources who provided the information (specify):		
Name and contact information of the person completing these clinical trials:	Designation:	Date/ Time:

Instructions- Attach copies of ALL available documents (including case sheets, discharge summary, case notes, laboratory reports and autopsy reports, prescription for concomitant medications) and then complete addtitional information NOT AVAILABLE in existing documents, i.e,

- **If patient has received medical care-** attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write the only information that is not available in the attached document below.
- **If the patient has not received medical care-** obtain history, examine the patient and write down your findings below. (add additional sheets if necessary).

Provisional/ Final Diagnosis:

SECTION D- Details of vaccine provided at the site linked to AEFI on corresponding day											
Number immunized for each antigen at session site. Attach record.	Vaccine name										
	Number of doses										

a)	When was the patient immunized? (P) tick the box below and respond to all questions ☐ within the first vaccination of the session ☐ within the last vaccination of the session ☐ Unknown	
	In case of multidose vials, was the vaccination given ☐ within the first few doses of the vial administered ☐ Within the last doses of the vial administered ☐ Unknown?	
b)	Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes* / No
c)	Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes*/ No/ Unable to access
d)	Based on your investigation, do you feel that the vaccine's physical condition (eg. colour, turbidity, foreign substance etc.) was abnormal at the time of administration?	Yes*/ No/ Unable to access
e)	Based on your investigation, do you feel that there was an error in vaccine reconstitution/ preperation by the vaccinator (eg. Wrong product, wrong diluent, improper mixing, improper syringe filling etc.)	Yes*/ No/ Unable to access
f)	Based on your investigation, do you feel that there was an error in vaccine handling (eg. Break in cold chain during transport, storage and/or immunization session etc.)?	Yes*/ No/ Unable to access
g)	Based on your investigation, do you feel that the vaccine was administered incorrectly (eg. Wrong dose, site or route of administration, wrong needle size, not following injection practice etc.)	Yes*/ No/ Unable to access
h)	Number immunized from the concerned vaccine vial/ampoul	
i)	Number immunized with the concerned vaccine in the same session	
j)	Number immunized with the concerned vaccine having same batch number at other location. Specify locations:	
k)	Could the vaccine given to this patient have a quality defect or is substandard or falsified?	Yes*/ No/ Unable to access
l)	Could this event be a stress response related to immunization(eg. Acute stress response, vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	Yes*/ No/ Unable to access
m)	Is this case a part of a cluster?	
	i. If yes, how many other cases have been detected in the cluster?	
	a. Did all the cases in the cluster receive vaccine from same vial?	Yes*/ No/ Unable to access
	b. If no, number of vials used in the cluster?	

it is compulsory for you to provide explanations for these answers separately

SECTION E- Immunization practices <u>at the place(s) where concerned vaccine was used</u> (Complete this section by asking and/or observing practice)
Syringes and needles used:
• Are AD syringes used for immunization?

If no, specify the type of syringe used ☐Glass ☐ Disposable ☐Recycled disposable ☐Other _____			
Specific key findings/additional observations and comments:			
Reconstitution: (complete only if applicable, P NA if not applicable			
Reconstitution procedure (P)	Status		
• Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
• Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
• Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
• Separate reconstitution syringe for each vaccination?	Yes	No	NA
Are the vaccines and diluents used the same as those recommended by the manufacturer	Yes	No	NA
Specific key findings/additional observations and comments:			
Injection techniques in vaccinator(s): (Observe another session in same locality- same or different place)			
• Correct dose and route?	Yes/ No		
• Time of reconstitution mentioned on the vial?(in case of freeze dried vaccine)	Yes/ No		
• Non-touch technique followed?	Yes/ No		
• Contraindications screened prior to vaccination?	Yes/ No		
• How many AEFI reported from the centre that distributed the vaccine in last 30 days?			
• Training received by the vaccinator? (if yes, specify the date of last training _____)	Yes/ No		
Specific key findings/additional observations and comments:			

SECTION F-Cold Chain and Transport (Complete this section by asking and /or observing practice)	
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/ No/ Unkn
○ If 'yes', was there any deviation out side of 2-8degrees after the vaccine was placed inside?	Yes/ No/ Unkn
○ If 'yes', provide the details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluent and syringes followed?	Yes/ No/ Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes/ No/ Unkn
• Was any partially used reconstituted vaccine in the refrigerator?	Yes/ No/ Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen)in the store?	Yes/ No/ Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes/ No/ Unkn

Specific key findings/additional observations and comments:	
Vaccine Transportation	
• Type of vaccine carrier used?	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes/ No/ Unkn
• Was the vaccine carrier returned from the site on the same as vaccination?	Yes/ No/ Unkn
• Was a conditioned ice pack used?	Yes/ No/ Unkn
Specific key findings/additional observations and comments:	

SECTION G- Community Investigation (Please visit locality and interview parents /others)
Were any similar events reported within the time period similar to when the adverse event occurred and in the same locality? Yes/ No/ unknown. If yes, describe.
If yes, how many events/ episodes?
Of those effected, how many are • Vaccinated _____ • Not vaccinated _____ • Unknown _____
Other comments:

SECTION H- Other findings/Observations/Comments

Patient Summary Report

Name:	**NID:**	**Age:**
Date and Time of Vaccination:		
Date of Presenting Complaints:		
Presenting Complaints:		
Underlying conditions and Medications: **Previous Allergies:** **Significant Past History:**		
If it's a sudden death, please write the patient's condition from the time of vaccination		
Working diagnosis:		
Treatments given:		
Progression:		
Final diagnosis:		
Plan:		

Treating Doctor:
Signature:

Appendix 3: AEFI monthly compilation form and Line listing

National Immunization Program

AEFI MONTHLY Compilation Form

Source	S.No	Name/ID	AEFI Reporting ID Number	Patient Location (Island)	Sex (M/F)	Pregnant (Y/N)	Lactating (Y/N)	Age	Vaccine Brand	Manufacturer	Dose	Vaccine Batch Number	Diluent Batch Number	Adverse Event	Place of Vaccination	Date of vaccination	Date of onset	Date of Notification	Date of Reporting	Serious(Y/N)	Reason for serious	Outcome	Autopsy Conducted (Y/N/NA)	Reported by	Reporter Location	Investigation planned Y/N)	Date report recorded at National level

National Immunization Program

AEFI MONTHLY Compilation Form

Atoll: ____________________ Reporting Epidemiologic week no: ______ Month___________ Year___________

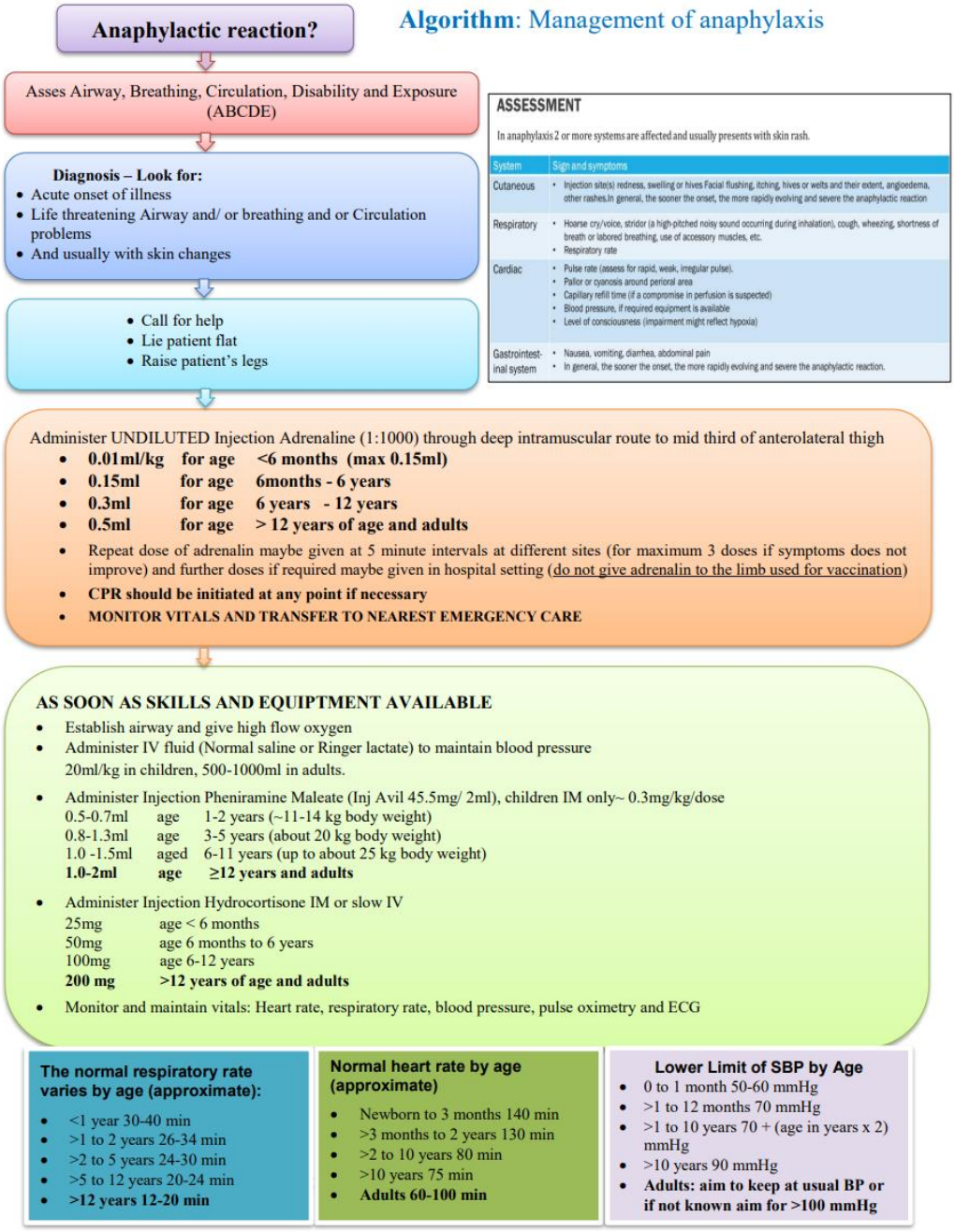
No. of Reporting sites:______ No. reported:_________ No. reported in time:_________ No. of AEFI cases: (If none, write "0")

* Write any of the following: severe local reaction, abscess, BCG lymphadenitis, hospitalization, encephalitis/encephalopathy, loss of consciousness/shock, high fever, convulsion, death, AFP, other (describe) (ވެކްސިން ދިން ހިސާބު ދުޅަވެ އަދި ދަތުރުވުން، ބީ.ސީ.ޖީ ލިމްފެޑެނައިޓިސް، ވެކްސިން ދިނުމުގެ ފަހުން ހޮސްޕިޓަލްގައި ... އެހެނިހެން (ބަޔާންކުރޭ)
*Number of of serious AEFIs reported
** FHW, CHW, MA, Pharmacist, Nurse, Doctor, Other (describe) ވެކްސިން ދިނީ: ޢާއިލާގެ އެޑިއުކޭޓަރ، ކަމިއުނިޓީގެ ސިއްޙީ އެޑިއުކޭޓަރ، ފާމަސިސްޓް، ނަރުސް، ޑޮކްޓަރ، އެހެން ފަރާތެއް (ބަޔާން ކުރޭ)
*** Recovered, Died, Residual problem – describe (ރަގަޅު ވުން، މަރުވުން، އެހެން ގޮތެއް (ބަޔާން ކުރޭ)
Comments:

Prepared by: Name:	Designation:	Signature:	Date:	Submitted by: Name:	Designation:	Signature:	Date:

immediate report when a case is found, including monthly "0" reporting, is important to reach National Immunization program.

Appendix 3: Anaphylaxis management guideline



Appendix 4: Response to Sudden death of unknown cause guideline

National Immunization Program (NIP) should be informed by phone immediately (Tel no 7205530), when dealing with a suspected sudden death of unknown cause in a vaccinated person and for newly introduced vaccines such deaths should be reported at least for one year following receipt of the vaccination. When the status of vaccination is unknow with regard to newly introduced vaccines, it is advised follow the procedure as per a vaccinated person. The Clinical Surveillance focal point in the institute and public health units should be involved. Follow the guideline below in assessing such patients, the aim is to get information and laboratory evidence for the causes of sudden deaths.

1. **Take proper history and do examination of the patient**

   Take proper history from the time of vaccination to the event/sudden death. Include underlying condition of patient and any medication the patient has been on. Any change in routine such as activity, diet, bowel and bladder habits etc.

   Negative history also should be taken to rule out sudden cardiac events, sudden neurological events, trauma, ingestion or history suggestive of any infective pathology. As available review and evaluate the medical documents of last 3 months to find out probable cause of death. Do all baseline investigations and other investigations as relevant to history. **Clinical Examination** Clinical examination should be done to corroborate with the history.

2. **Investigation**

- **For all the cases of sudden deaths these investigations should be done. If the relevant investigations are not available please obtain the samples and coordinate with central level-**
  - ✓ Blood for CBC, and peripheral smear if available
  - ✓ ESR,
  - ✓ CRP (if available),
  - ✓ Sodium, Potassium,
  - ✓ ALT, AST,
  - ✓ BUN and Creatinine,
  - ✓ RBS and Hb1Ac if available,
  - ✓ **PCR COVID,**

- ✓ CXR,
- ✓ Blood sample for toxicology. In addition, gastric lavage or urine sample can also be obtained for toxicology (according to history and sample can be sent in coordination with NIP to Central level),
- ✓ Cardiac enzymes
- ✓ Urine (catheterized) routine and culture (keep sample in fridge if culture not available),
- ✓ Blood culture (if bottle available),
- ✓ Stool routine, culture and keep an extra stool sample in fridge (if loose stools)
- ✓ CT brain if need to rule out intracranial pathology (if facility available)

- **Store extra blood samples:**
  - Two extra serum sample and to be kept for further investigation (stored at 2 to 8 degrees Celsius and transported to IGMH as soon as possible; central lab to store sample at -70 degrees Celsius)
  - One anticoagulant EDTA sample
- **Other investigations according to history and presentation of the person, please kindly coordinate with NIP, AEFI team (7205530) regarding sudden death cases.**

3. **Details and status of all the people vaccinated with the same vial to be collected by public health units/ relevant institutes.**

Appendix 4: AEFI investigation check list (WHO)

https://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_Aide_Memoire.pdf

WORLD HEALTH ORGANIZATION

AEFI Investigation

AIDE MEMOIRE

An **adverse event following immunization (AEFIs)** is a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization. Programmes providing immunization services should include **a system for AEFI detection** and **reporting, investigation and management, data analysis, corrective action, relevant communication** and **evaluation of the system**.

The ultimate **goal** of an investigation is to determine whether the vaccine or immunization process is responsible for the reported event(s) or to find another and correct it if possible, and reassure the public.

There are 4 possible causes of AEFI:

Vaccine reaction: event caused by some component of the vaccine – the active component of the vaccine itself, the preservative, the stabilizer or other. The majority of vaccine reactions are "common" and expected, mild, settle without treatment and have no long-term consequences. More serious reactions are very rare – usually of a fairly predictable (albeit extremely low) frequency;

Programme error: event caused by error in vaccine preparation, handling or administration;

Coincidence: event where something happens after the immunization but is not caused by the vaccine or the programme; and

Injection reaction: event arising from anxiety about the injection (needle).

The **purposes of investigating AEFI** cases are:

1) to confirm a reported diagnosis of AEFI and clarify the details and outcome;
2) to determine whether unimmunized persons are experiencing the same medical event(s);
3) to investigate the link between the vaccine given and the AEFI ;
4) to determine the contribution of operational aspects of the programme to the reported AEFI;
5) to determine whether a reported event was isolated or part of a cluster;
6) to determine the cause of the AEFI so as to provide the best intervention/medical care and take any further action deemed necessary.

In most cases, a preliminary **investigation** of an AEFI can be made by the health worker who detected the case, e.g. a health centre staff member or a nurse or physician in a hospital.

Serious AEFI cases or **AEFI clusters** should be investigated immediately with involvement from central levels including epidemiological and/or clinical expertise. A cluster of AEFIs can be defined as two or more cases of the same adverse event related in time, place or vaccine administered.

Inadequate planning or response may lead to a crisis with loss of confidence in the vaccination service. It is essential that programme managers:

1) **anticipate** the crisis and be prepared to deal with it when it occurs;
2) **verify** the facts of any event before making any public statement;
3) **are familiar with a plan** for reacting to any crisis should it happen. If no plan exists programme managers should develop one;
4) **be well informed** so that appropriate national and regional managers can be rapidly briefed to take charge and deal with political and media enquiries.

☑ Checklist

1. Be prepared

- ☐ Read the resource documents on reporting, management and investigation of AEFIs.
- ☐ Develop standards: case definitions for reportable AEFIs, use of reporting forms and investigation procedures.
- ☐ Designate and train staff to conduct an AEFI investigation using the investigation form.
- ☐ Train staff on how to collect specimens.
- ☐ Establish procedure, criteria and designated person for notifying WHO and UNICEF (if UN- supplied vaccine) or other relevant party depending on procurement mechanism
- ☐ Establish a National Technical Advisory Committee with representation from major medical organizations
- ☐ Identify a spokesperson for public communications.

2. Receiving a report

- ☐ Ensure immediate reporting of most serious events and rapid attention to reports received
- ☐ Verify the information in the report and classify and assess the AEFI using established case definitions. Decide whether it needs further investigating.
- ☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person

3. Investigate and collect data

- ☐ Ask about the patient
- ☐ Ask about the vaccine and other drugs potentially received
- ☐ Ask about other vaccinees
- ☐ Ask about immunization services
- ☐ Observe the service in action
- ☐ Ask about cases in unvaccinated persons
- ☐ Establish a more specific case definition if needed
- ☐ Formulate a hypothesis as to what caused the AEFI

Collect specimens if appropriate:

- ☐ from the patient
- ☐ the vaccine (and diluent if applicable)
- ☐ the syringes and needles

4. Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

5. Analyze the data

- ☐ Review epidemiological,clinical, and laboratory findings
- ☐ Summarize and report findings

6. Take action

- ☐ Communicate with health staff
- ☐ Communicate findings and action to the parents and public
- ☐ Correct problem (based on the cause) by improving training, supervision, and/or distribution of vaccines/injection equipment
- ☐ Replace vaccines if indicated

Key data to be collected

1) **Data on each patient**
- demographic data about patient, including a unique case number, age, sex, place of residence, family history;
- history of patient's present illness - symptoms and when each appeared and its duration, treatment, outcome, diagnosis;
- history of patient's past illnesses e.g., reactions to previous vaccine doses, drug allergies;
- pre-existing disorders, current medications;
- immunization history - vaccine, number of doses received, date, and place of last immunization or immunizations, mode and site of administration;
- laboratory results about blood, stool, or other samples, if appropriate and available
- full autopsy report with toxicological screening and histo-pathological analysis
- look for common environmental exposures between patients.

2) **Data about the vaccine(s) (and diluent if applicable) administered to the patient**
- Lot number(s)
- Expiry date(s)
- Manufacturer(s)
- Vaccine storage
- Identify where the vaccine(s) was distributed
- Whether other children were immunized with same lot or same vial at same session and elsewhere
- Results of procedures to control vaccine quality
- Laboratory test results about vaccine, if appropriate.

3) **Programme-related data.**
- Common practices in storing and handling vaccines, and vaccine administration in the health centre in which the suspected immunization (or immunizations) were given. This may help identify products mistakenly used instead of vaccine or diluent

4) **Background data**
- Establish if cases have been reported from elsewhere and actively look for additional cases among other vaccinees and at large in the community

Role of the district/regional manager

1) Training
Staff should be trained in diagnosing, treating and reporting of AEFIs, and differentiating between mild, non-significant reactions and more serious events.

2) Supervision
Non-serious AEFIs (e.g. abscesses) reported by peripheral health workers should be reviewed with training during site visits.

3) Investigation and collection of data
Following a report of a serious AEFI, the manager should be responsible for investigation, collection and reporting of data. This may be under the overall supervision of a national team.

4) Communication
The manager or designated person should set up the means for continuous communication between health workers and the community, directly and through the media. The public should be informed frequently about what is being done during an investigation and reassured where necessary.

5) Correction of the problem
If an AEFI was caused by programme error the actions to be taken will probably include one or more of the following:

- **Logistics**
  Improving logistics will be the appropriate response if programme errors can be traced to the lack of appropriate supplies or equipment, or to a failure in the cold chain.
- **Training**
  Solving operational problems through training will deal with lack of skills and knowledge and with poor attitude.
- **Supervision**
  Regular supervision and intensified when needed e.g., problems detected in reporting or programmatic errors identified.

Did the vaccine or its delivery cause the reactions?

It will be necessary to determine if there is a causal association between the vaccine and the adverse event. In each case the following should be considered:

Consistency of findings – are all reported AEFIs the same?

Temporal sequence – confirm that the symptoms of AEFI occurred only after, not before, the vaccine was given and if the vaccine-event interval is compatible with a vaccine reaction

Biological plausibility – does the medical event seem plausibly due to an effect of the vaccine or other concomitant or preceding conditions?

Previously known reaction – check if this type of reaction is known to be related to the vaccine and with which frequency

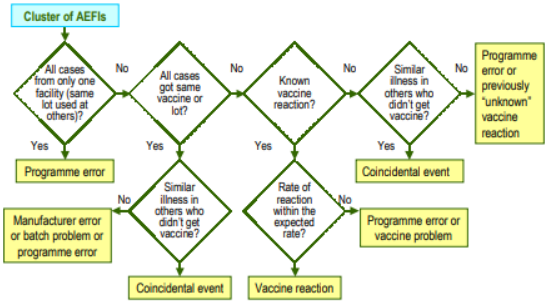
Specificity and strength of association – establish if the same events are being reported in unvaccinated persons and if so, how often and if the cluster is limited to one health center or not

Concomitant or preceding conditions

AEFI evaluation requires a 2 by 2 table of exposures and outcomes and data should be collected in order to more fully complete the table and calculate a risk of event from receipt of the vaccine i.e. (a/a+c)/(b/b+d). Cell a represents case reports only

	Possible Adverse Event	No Adverse Event
Vaccinated	a	c
Unvaccinated	b	d

Suggested steps for the identification of the most likely cause of a cluster of AEFIs



Words of advice

- The investigation should start within 24 hours of notification
- There is seldom need to test the vaccine unless clearly indicated by the epidemiologic investigation, but cold chain should be maintained
- A national committee can be very helpful in reviewing the outcome of the investigation and communication of findings
- Access medical files
- Rule out alternative aetiologies than the vaccination. The fact that an adverse event of the same nature has been previously related to a particular vaccine does not always mean that the case under investigation is also related to the vaccine
- Have direct discussions with the patients or parents if possible

Additional information on the definitions, monitoring, management and investigation of AEFIs can be found on the World-Wide Web at www.who.int/immunization_safety/en

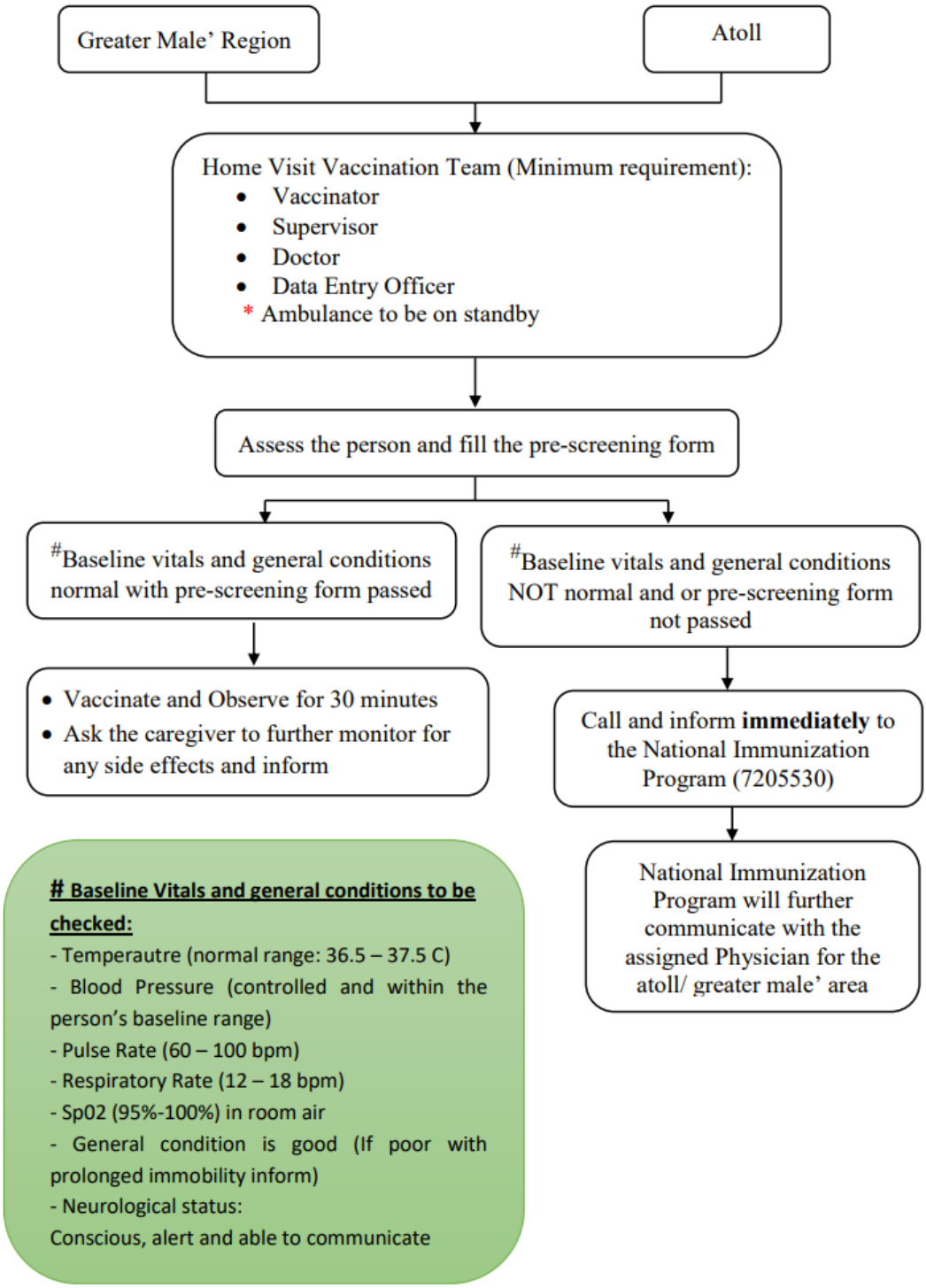
Vaccine Assessment and Monitoring
Department of Immunization, Vaccines, and Biologicals
World Health Organization
20 avenue Appia, 1211 Geneva 27, Switzerland
Tel: +41 22 791 4468 Fax: +41 22 791 4210
Email: immunizationsafety@who.int

ASSESSMENT OF IMMOBILE, FRAIL ELDERLY PERSONS PRIOR TO COVD-19 VACCINE ADMINISTRATION

Proper assessment should be done prior to vaccination for all individuals (see algorithm below). This is especially important for people who are immobile and for those frail elderly persons with poor mobility, impaired communication, multiple chronic conditions and requiring assistance in self-managing. People with these conditions could develop a life-threatening situation even with a mild AEFI such as vomiting or diarrhoea. Hence a proper assessment must be done prior to administration of COVID-19 vaccine to these individuals.

1. Prior to vaccination monitor vitals and document the required information on prescreening form.
2. Assess social support available at home (availability of a family member at home as a care giver to look after the patient in the days following vaccination). Vaccination should be deferred until family can guarantee good support for the patient after vaccination.
3. Explain that in a patient who have poor level of alertness minor events such as vomiting may lead to a life-threatening situation. In such patients if vomiting occurs, caregivers should pay extra attention and care to avoid vomitus aspiration. Please inform National immunization program (phone 7205530) prior to vaccinating anyone in this category.
4. Defer vaccination if patient has any new symptoms currently or any change in the baseline status, or history of admission to hospital within the past 1 month. If history of recent admission should be informed to National Immunization program prior to vaccination by phone 7205530.
5. Explain the common adverse effects of vaccine such as fever, loose motion and vomiting
6. Hydrate the person with liquids (avoid sugary drinks).
7. Give properly made ORS if loose motion (do not add anything else to the ORS including glucose powder)
8. Any food or drink should be given in propped up position.
9. If the person is having nausea or vomiting keep the person on to one side, monitor well and advice to take to the health facility.
10. Inform the caretaker to take to the nearest health facility as soon as possible if any new symptoms develop or any change in condition of patient after vaccination

Process flow for immobile, frail elderly persons prior to vaccine Administration



Pre-Vaccination Screening for the Elderly

(Please attach this sheet with the consent form)

Patient Details:

Name:	Age:	ID/PPN:

Diagnosis:		
Current Medication:		
Apparent State of Health:	Please tick where appropriate	Others:
Bedridden:	Yes / No	
Wheelchair Bound:	Yes / No	

Pre-vaccination Screening for Elderly

Section No:	Components to be checked	**Please circle where appropriate**
1	Conscious level:	
	Awake :	Yes / No
	Alert:	Yes / No
	Responsive	Yes / No
	Lethargic:	Yes / No
	If others, Please specify:	
If the patient has poor level of alertness, inform the National Immunization Program **prior** to Vaccination (7205530)		
2	Vitals checked: (Also, Please specify)	Yes / No

3	Does the patient have new symptoms or change in baseline status within the last 2 weeks:	Yes / No
	Has the patient been admitted to the hospital within the past 2 weeks:	Yes / No
(if any answer in the section 3 is yes, please inform NIP via the contact number provided **prior** to vaccination)		
4	Social Support Availability at home:	Yes / No
	Name of the caretaker:	
	Relationship to the Patient:	
	Is it adequate support for the patient:	Yes / No
5	**Management of side effects; The patient is given the following advise**:	
	Give properly made ORS in a case of loose motion and do not add anything else to the ORS (not even glucose).	Yes / No
	Any food or drink should be given in a propped up position.	Yes / No
	If the patient is having nausea or vomiting, keep the patient on one side, monitor well and give advice to take to the health facility.	Yes / No
	The caretaker and the patient are informed to visit the nearest hospital as soon as possible if any new symptoms develop or any change in the condition of the patient after vaccination.	Yes / No

DECISION MADE REGARDING VACCINATION:

Was the person vaccinated?: Yes / No
If no, what was the reason:

Was the NIP informed?:

IN CASE OF AN EMERGENCY, PLEASE CONTACT:
National Immunization Program via - 7205530

FOR OFFICIAL USE ONLY:
Name of the official:
Designation:
Date:
Signature