National Guideline on Surveillance of Adverse Events Following Immunization

2nd Edition 2015

Royal Government of Bhutan

Ministry of Health

Vaccine Preventable Disease Program

Department of Public Health

Ministry of Health

FORWARD

Although the manufacture of Vaccines Produce Vaccines strictly following safety norms and ensure effectiveness with the current technology available, no biological product is 100% safe & effective. Vaccines can cause minor and serious adverse events. The serious adverse events where a vaccine is incriminated are very rare.

Since Adverse Events Following on Immunization AEFI Surveillance in Bhutan was initiated from 2003. AEFI surveillance allows the immunization programme to monitor the occurrence of adverse events and to identify the true from the false AEFI. The system will also ensure quality by monitoring immunization error, increase public confidence, and help to develop capacity to manage 'crisis' events within the immunization programme. It is important AEFI are reported and investigated as they require response to all corrective measures to prevent additional cases. This will boost public confidence in the program and also help to improve the quality of the program in the long run.

Hope, that this manual will guide the health workers at all levels to strengthen Adverse Events Following Immunization (AEFI) Surveillance system

Tashi Delek!

(Dr. Dorji wangchuk)

Secretary

Ministry of Health

Thimphu.

CONTRIBUTORS

1. Dr. Dr. K. P. Tshering,
   President, University of Medical Sciences
2. Dr. T.B.Rai
   Medical Specialist, RBA Lungtenphu Hospital
3. Mr. Sonam Dorji
   Drug Controller, Drug Regulatory Authority
4. Dr. Mimi Lhamu Mynak,
   HoD, Department of Pediatric, JDWNRH
5. Dr.Tshokey,
   HoD, Clinical Laboratory, JDWNRH
6. Mrs. Sonam Wangmo
   Health Assistant, Gelephu Regional Referral Hospital
7. Mr. Dawa gyeltshen
   Health Assistant, BHU
8. Mr.Sangay Phuntsho
   Programe Officer, VPD Program
9. Mr.Tshewang Dorji Tamang,
   Sr. Programme Officer, VPD Program

EDITOR

Mr. Sonam Wangchuk,

Chief Laboratory Officer, Public Health Laboratory, Ministry of Health

TABLE OF CONTENT

LIST OF TABLES AND FIGURES

LIST OF ANNEXURE

ABBREVIATIONS

AEFI	Adverse Events Following Immunization
AFP	Acute Flaccid Paralysis
BCG	Bacillus Calmett Guerin- vaccine for tuberculosis (TB)
ORC	Out Reach Clinic
DRA	Drug Regulatory Authority
DHO	Dzongkhag Health Officer
ADHO	Assistant Dzongkhag Health Officer
DTP	Diphtheria Tetanus Pertussis
DT	Diphtheria Tetanus
VPDP	Vaccine Preventable Disease Program
HA	Health Assistant
DIR	Detailed investigation report
Hep.B	Hepatitis B
Hep.C	Hepatitis C
HIV	Human Immunodeficiency Virus
ILR	Ice Lying Refrigerator
MoH	Ministry of Health
OPV	Oral Polio Vaccine
IPV	Inactivated Polio Vaccine
BHU	Basic Health Unit
WHO	World Health Organization
UNICEF	United Nation Children Fund
VVM	Vaccine Vial Monitor
RRH	Regional Referral Hospital
NCIP	National Committee for Immunization Practice

1. INTRODUCTION

Immunization is the most effective preventive intervention and widely used to protect the individual and the public from vaccine preventable diseases. Modern vaccines are safe and safety quality, efficacy (level of protection) and effectiveness (disease reduction) will continue to improve with time as the technology improves, however, no vaccine is entirely without risk. As more new vaccines would be added into the programme including new vaccines for emerging diseases, the risk of adverse events following immunization (AEFIs) would increase with increased use of vaccines.

AEFI ranges from mild side effects to life-threatening illnesses but rare and majority of AEFI are merely coincidences. However, irrespective of the cause, confusion is created among the parents/people to the extent that they may refuse further immunizations for their children leaving them susceptible to vaccine preventable diseases which are more disabling and life threatening. To improve public confidence in immunization programme, health professionals at all levels should be familiarized with all aspects of immunization. Furthermore, health professionals should be equipped to respond to any concerns of the public about immunization safety, including vaccine safety concerns. Any AEFI reports that concerns the public about the safety of vaccines should timely respond as well as communicate promptly to protect the public and preserve the integrity of the immunization programme.

To address immunization safety and increase acceptance of immunization, AEFI surveillance must become an integral part of the immunization programmes. AEFI surveillance like any other disease surveillance is systematic collection of data on events following immunization to help planning proper management of AEFIs, regaining of public confidence on immunization and avoids inappropriate responses to AEFI’s reports.

With easy access to information and communication technology, there is increased public alert on vaccine safety and this invariably creates more demand on vaccine quality and safety by both service providers and public. With this complexity, true or possible vaccine link and prove coincidence need more detailed investigations, i.e causality assessment. Causality assessment is an evidence based approach with more scientific analysis of data, often requires a wide ranges of expert's opinions, even further research studies

General Objective

To strengthen and improve efficiency of AEFI reporting system thereby ensure immunization safety to all recipients and sustain high vaccine coverage and quality of immunization services at all levels.

Specific Objectives:

- To detect and timely identify problems related to vaccines inherent properties
- To detect, correct and prevent immunization related errors
- To identify clustering or unusually high rates of both serious and mild AEFI
- To conduct causality assessment of all serious AEFI and events of public concern
- To estimate AEFI rates in the population
- To effectively communicate and sensitize parents, community, media and other stakeholders on AEFIs and the immunization service.

1.3. Key elements of an effective AEFI surveillance system include:

1. Early detection and notification of AEFI.
2. Timely and effective analysis/ evaluation of data/information.
3. Conducting timely and comprehensive investigation and causality assessment.
4. Timely follow up actions based on investigation and causality assessment findings.
5. Dissemination of investigation and causality assessment findings to responsible persons, health centers and relevant stakeholders.
6. Effective communication with public and other stakeholders.
7. Provide training for health professionals periodically and as and when required.

2. ADVERSE EVENTS FOLLOWIGN IMMUNIZATION (AEFI)

The national immunization programmes use vaccine that is extremely safe and effective but vaccines being biological product, no vaccine are perfectly safe. In addition, the procedure of providing immunization is a potential source of adverse events. An adverse event following immunization (**AEFI**) is defined as "**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.

Reported adverse events can either be true adverse events, i.e. really a result of the vaccine or immunization process, or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. Accordingly AEFIs were classified into five categories (Table 1).

Table 1: Classification of adverse events following immunization

Type of AEFI	Definition
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine (e.g. adjuvant, preservative and stabilizer). This is due to the inherent properties of the vaccine and if this can be either due to product defect or without any quality defect.
Immunization error	An event caused by an error in vaccine preparation, handling or administration.
Coincidental	An event that occurs after immunization but is not caused by the vaccine. This is due to a chance temporal association
Injection Reaction	Event caused by anxiety about, or pain from the injection itself rather than the vaccine
Unknown	The cause of the event cannot be determined

However, the Council for International Organizations of Medical Sciences (CIOMS) / WHO revised this classification concerning particularly cause-specific categorization of AEFIs and a **new categorization** was introduced in 2012 (Table 2).

Table 2: Cause –specific categorization of adverse events following immunization (CIOMS/WHO, 2012)

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

2.1. Vaccine Reaction

A vaccine reaction is an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. The new cause-specific category categorizes vaccine products into two types of possible vaccine reactions.

(i) **Vaccine product related reaction -** is a vaccine reaction an individual's response to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly.

(ii) **Vaccine quality defect-related reaction;** is the vaccine quality defect during manufacturing process which will have an impact on individuals response and thereby increased risk of adverse vaccine reactions. (*Details are available in the "Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012).*

Vaccine reactions may also be classified into common, minor reactions and rare more serious reactions. Most vaccine reactions are minor and settle on their own but some vaccines may cause rare serious reactions which need management.

2.1.1. Common, minor vaccine reactions: These include common mild side-effects, such as local reactions (pain, swelling and/or redness), fever and systemic symptoms (e.g. vomiting, diarrhea, malaise), which can result as part of the normal immune response to the vaccine. Some of the non-antigenic vaccine components (e.g. adjuvant, stabilizers or preservatives) can also cause some of these vaccine reactions. The frequency and nature of common non serious vaccine reactions are outlined in Table 3.

2.1.2 Rare serious vaccine reactions

Serious vaccine reactions [seizures, thrombocytopaenia, hypotonic hyporesponsive episodes (HHE), persistent inconsolable screaming] are rare and may or may not have long term sequelae. For example serious reactions such as anaphylaxis though potentially fatal are treatable without leaving any long-term effects. An increase in the expected frequency of rare serious reactions may indicate either a problem with a specific batch of vaccine or a programme error. It is important to reiterate that not all AEFIs are actually caused by vaccines.

As defined by the Uppsala Monitoring Centre (UMC), a serious adverse event or reaction is any untoward medical occurrence following any dose of vaccine that

- Results in death.
- Requires hospitalization or prolongation of hospital stay.
- Results in persistent or significant disability/incapacity are life-threatening.

Case definitions for these adverse events or reactions are given in **Annex 1**. ***To determine the exact cause of serious AEFIs, such suspected vaccine adverse events should be reported and investigated.***

The information in tables 3 and 4 can be used to:

- Anticipate the expected rate and type of reactions
- Identify events that are probably unrelated to immunization (outside the time window or not clinically compatible)
- Compare reported with expected rates of reactions (the efficiency of reporting)
- Trigger an investigation if the reported rate is greater than the expected rate for minor reactions or if a major reaction is reported.

Table 3: Frequency and nature of non-serious reactions

Vaccine	Local reaction (pain, swelling, redness)[1]	Fever (greater than 38 ^{0}C)	Irritability, malaise and non-specific symptoms
BCG	Common 90%-95%		
Hepatitis B	Adults up to 30% Children up to 5%	1 – 6%	
Hib	5 -15 %	2-10%	
Measles/MMR	Up to 10%	5-15%	Up to 5%(rash)
OPV	None	Less than 1%	Less than 1%[2]
Tetanus/DT/Td	Up to 10%[3]	Up to 10%	Up to 25%
Pertussis (DPT-Whole cell)[4]	Up to 50%	Up to 50%	Up to 60%

[1] Local reactogenicity varies from one vaccine brand to another, depending on the strain and the number of viable antigen in the vaccine.

[2] Rate of local reactions are likely to increase with booster doses, up to 50 -85%.

[3] Diarrhoea, Headache and/or muscle pain.

[4] When compared with the whole cell pertussis vaccine, acellular pertussis vaccine rates are lower.

Table 4: Frequency and nature of serious vaccine reactions

Vaccine	Reaction	Interval between vaccination and onset	Number of events per million doses
BCG	Suppurative adenitis	2-6 months	100-1000
	BCG Osteitis	Up to several years	-
	Disseminated BCG infection	1-12 months	-
Hib	None known	-	-
Hep B	Anaphylaxis	0-1 hour	1-2
Measles/ MMR[a]	Febrile seizures	5-12 days	330
	Thrombocytopenia (low platelets)	60 days	30
	Anaphylaxis	0-1 hour	1
OPV	Vaccine-Associated Paralytic Poliomyelitis	4-30 days	Up to 0.4 [b]
Tetanus	Brachial Neuritis	2-28 days	5-10
	Anaphylaxis	0-1 hour	1-6
	Sterile abscess	1-6 weeks	6-10
DPT	Persistent (>3hours) inconsolable screaming	0-48 hours	1,000-60,000
	Seizures	0-3 days	600[c]
	Hypotonic Hypo Responsive Episode (HHE)	0-24 hours	30 - 990
	Anaphylaxis/Shock	0-1 hour	1 -6
Japanese Encephalitis	Serious allergic reaction	0 – 2 weeks	10 - 1000
	Neurological events	0 – 2 weeks	1 – 2.3

[a] Reactions (except anaphylaxis) do not occur if already immune (~ 90% of those receiving a second dose): children over six years are unlikely to have febrile seizures

[b] VAPP risk is higher for first dose (12 per 1.4 to 3.4 million doses) compared to 1 per 5.9 million for subsequent doses and 1 per 6.7 million doses for subsequent contacts.

c Seizures are mostly febrile in origin, and the rate depends on past history, family history and age, with a much lower risk in infants under the age of 4 months

2.1.3. Prevention of vaccine reactions:

Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, vaccines are contraindicated if there is;

1. Serious allergy to the vaccine (anaphylaxis) or its components (excipients)
2. Progressive neurological illness
3. Immunodeficiency (in the case of live vaccines)

Use of vaccines in pregnancy is limited or mostly not recommended. Vaccines which are recommended in pregnancy would benefit and protect both mother and the newborn. However, limited use of vaccines in pregnancy is largely due to the potential risk and harm to the fetus. Risk is mostly theoretical and limited to live attenuated vaccines which have demonstrated evidence of potential risk and harm. Risk or harm caused by killed or conjugated vaccines are either not proven or limited to case reports. Vaccine manufacturers highlight pregnancy as a contraindication not only due to lack of evidence in safety studies, but also as a precautionary measure against litigation.

2.2 Immunization error–related reactions

Immunization error was earlier categorized as “Programme errors” which occur as a result of inappropriate transport, storage, handling, preparation and administration of vaccines. Immunization errors can be prevented and controlled.

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. Immunization errors can also affect a stock of vaccines (e.g. by freezing vaccines during transport leading to an increase in local reactions in recipients). Table 5 outlines the most common programme errors leading to AEFI.

Table 5: Common program errors leading AEFI

Immunization error	Possible AEFI
Non-sterile injection	
• Contact of needle with unsterile surface e.g. finger, swab, table etc. • Contaminated vaccine or diluent • Administering injection over clothes	Infection e.g. local abscess at site of injection, sepsis
• Use of reconstituted vaccines • Beyond the stipulated time (6 hrs for BCG and Measles • Reuse of reconstituted vaccine at subsequent sessions	Toxic shock syndrome or death.
• Reuse of disposable syringe & needle	Blood-borne infections e.g. Hep B, HIV, Hep C etc.
Reconstitution error/ Wrong vaccine preparation	
• Reconstitution with incorrect diluent • Reuse of the reconstitution syringe	Less vaccine effectiveness.
• Drug substituted for diluents	Drug reaction; Death.
• Inadequate shaking of T-series vaccines	Local abscess.
Injection at incorrect site/route	
• Injection into gluteal region (buttocks)	Sciatic nerve damage, paralysis.
• BCG/T series vaccine given subcutaneously	Local reaction or abscess.
Vaccine transportation/storage incorrect	
• Administration of frozen and thawed freeze-sensitive vaccine	Increased local reaction such as sterile abscess. Less Vaccine effectiveness.
Contraindications ignored	
• DPT2 given after history of convulsions with DPT1	More severe convulsions

Prevention of Immunization errors (Programme errors):

- Vaccines must only be reconstituted with the diluent supplied by the manufacturer.
- Reconstituted vaccines should not be used for more than six hours after reconstitution.

- Reconstituted vaccines must be discarded at the end of each immunization session and never retained.
- No other drugs or substances should be stored in the same refrigerator where they are stored.
- Immunization staff must be adequately trained and closely supervised to ensure that proper procedures are being followed.

2.3 Coincidental Events

Children are usually given vaccines at an age when they are susceptible to many diseases. Thus, situations may arise when an adverse medical event is falsely attributed to the vaccine. Coincidental adverse events are clearly unrelated to vaccination. However, certain serious events may be blamed on the vaccine by parents or community because of its close temporal association with immunization, especially if the vaccinated individual was previously healthy. Therefore, responding to a community's concerns about immunization safety is important in maintaining confidence in the immunization programme. If the same event is also observed among the same age group and around the same time who did not receive the suspect vaccine(s), then a coincidental event is more likely. There may be other evidence showing that the event is not related to immunization. Therefore, knowledge of these background rates of disease and deaths, particularly *age specific disease incidence rates* are important and also helps to determine possible 'signals' and to correctly categorize them as coincidental events.

2.4 Immunization anxiety-related reactions

Individuals and groups can react in anticipation to an injection of any kind. This reaction may mimic an AEFI but is unrelated to the content of the vaccine. Commonly reported immunization anxiety-related reactions are:

2.4.1 Fainting - which is relatively common, but usually affects children aged over five years. Fainting does not require any management beyond placing the patient in a recumbent position. The likelihood of fainting can be anticipated when immunizing older children. Fainting can be reduced by minimizing stress in those awaiting injection through short waiting times, comfortable room temperatures, preparation of vaccine out of recipient view and privacy during the procedure. However, fainting may also occur sometime after immunization.

2.4.2 Hyperventilation – is as a result of anxiety about immunization that leads to specific symptoms (light headedness, dizziness, tingling around the mouth and in the hands). Younger children tend to react in a different way with **Vomiting**, a common anxiety symptom. These reactions are not related to the vaccine, but to the injection. Some individuals may be needle-phobic, aggravating such reactions. In a group situation, mass hysteria is possible, especially if a vaccine has fainted or has had some other reaction following vaccination. Clear

explanations regarding the immunization and calming vaccine recipient can reduce the likelihood of occurrence. It is important to note, faintish attack (syncope) can be misdiagnosed as anaphylaxis and health workers may administer a single dose of Adrenaline (intramuscularly) to a vaccine. To avoid such unnecessary medical emergency interventions, continued training and awareness for health professionals is necessary.

2.5. Special Issues

2.5.1 Serious Events: Serious AEFIs are defined as those that are life threatening and those that result in hospitalization (or prolonged hospitalization), disability (or have the potential to result in disability) or death. In addition, it is recommended that certain types of AEFI should be considered serious enough to warrant special attention in order to ensure immediate reporting when they are detected and response promptly including investigation and proper case management. These include AEFIs that may have been caused by immunization errors, occurring in cluster (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, HHE) and serious events of unexplained aetiology occurring within 30 days after a vaccination and events causing significant parental or community concern.

2.5.2 Cluster of AEFI

A cluster is defined as two or more cases of the same or similar event, which are related in time and have occurred within the same geographical unit or associated with the same vaccine, same batch number administered or same vaccinator or which had occurred during the same clinic session. For example, two or more cases of abscess occurring following one immunization session in a village; repeated cases of abscess following immunization by same vaccinator or same batch of the vaccine will be considered as clusters.

2.5.3 Signals

Signals are defined as a possible causal relationship of a reaction/event following a vaccine which was previously unknown or incompletely documented. Only a systematic causality assessment based on information/data collected through research methods can detect signals and establish causal relationships. This is important with new vaccines, particularly if introduced in a mass vaccination campaign.

3. AEFI SURVEILLANCE SYSTEM

3.1. AEFI surveillance:

An overview of the AFEI surveillance system is given in figure 1. All serious and non serious AEFI should be reported and investigated as per the list and case definition of AEFIs given in Table 6.

Any AEFI listed as per Table 6 should be registered in AEFI register and notified to DHO by health centers and to VPDP by referral hospitals in Adverse Events Following Immunization Notification Form (AEFI Form 1) as and when AEFI case is detected.

DHO will forward Notification Form for Adverse Events Following Immunization (AEFI Form 1) and also submit collated monthly Surveillance of Adverse Events Following Immunization (AEFI Form 2) to programme (VPDP). The respective DHO should develop and maintain AEFI data-based for their health monthly.

For AEFI investigation, Adverse Events Following Immunization Case Investigation Form (AEFI Form 3) should be used by investigating district AEFI team/clinicians/health workers.

Any deaths that have temporal relation with vaccine should be investigated using a separate investigation form given in Annexure 4 by district AEFI team/clinician.

Causality assessment should be done on all AEFI investigated at national level by AEFI committee.

AEFI information should be shared to DRA and other relevant stakeholders including WHO as and when required.

Feedback should be shared by programme to DHO or DHO to health centers as and when required (case based), quarterly and annually.

To detect AEFI, all children should be mandatory screened for AEFI following previous immunization in all health centers BHU's, district hospitals and referrals hospitals. Therefore it is important that relevant health workers in hospitals are made aware of AEFI and AEFI surveillance and their roles and responsibilities.

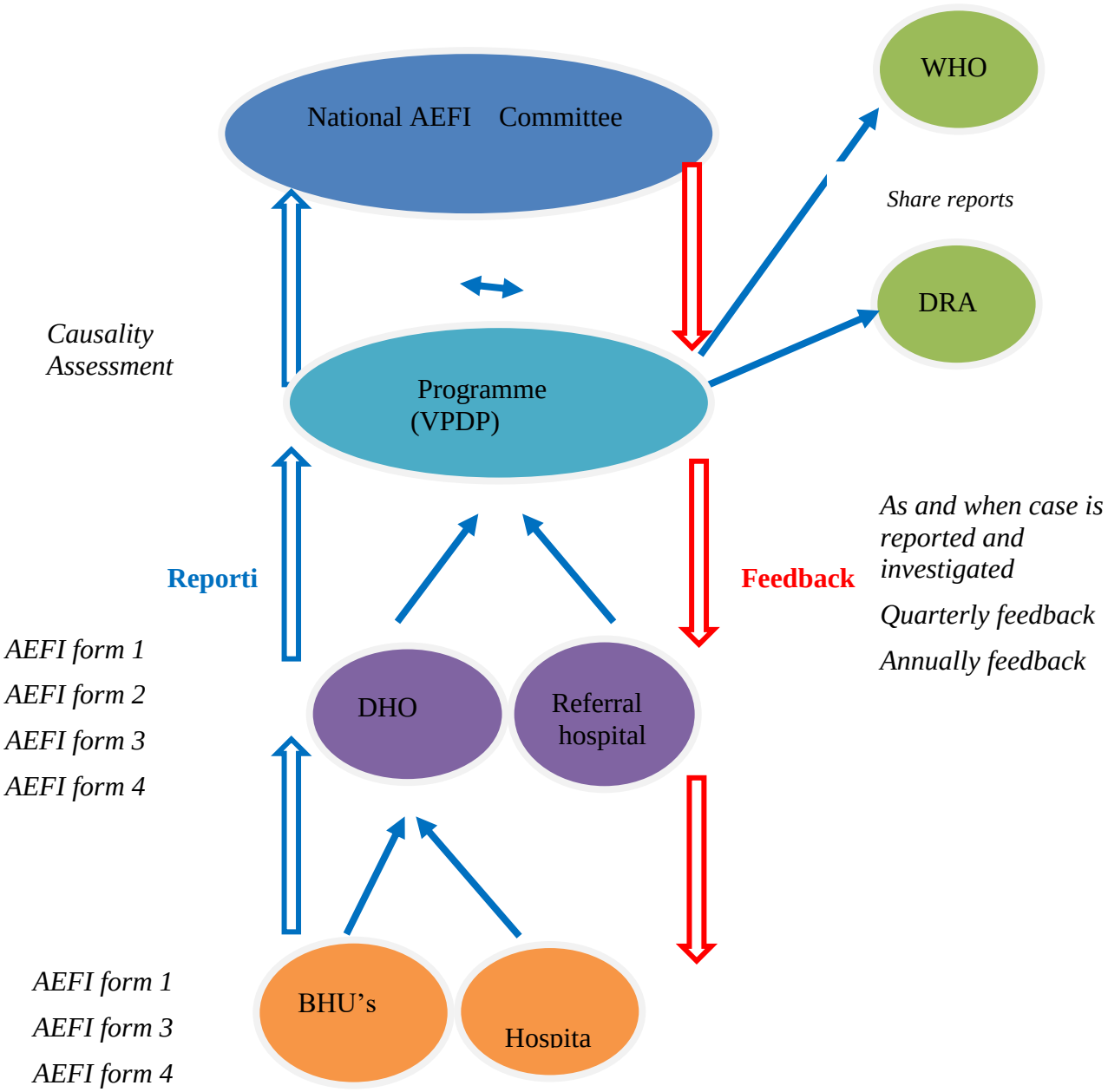


Figure 1: AEFI surveillance system

Table 6: List of AEFI and Case definitions to be used in surveillance

Local Adverse Events
a. Injection Site Abscess: Occurrence of a fluctuant or draining fluid filled lesion at the site of injection with or without fever. ➢ Bacterial: Existence of purulence, inflammatory signs, fever, positive Gram stain, positive culture, or finding of neutrophil predominance of content will support a bacterial site abscess, but the absence of some of these signs will not rule it out. ➢ Sterile: there is no evidence of bacterial infection following investigation
b. Lymphadenitis (includes supportive lymphadenitis): Occurrence of either: ➢ At least lymph node, 1.5cm in size (one adult finger width) or larger, or ➢ 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)
c. Severe local reaction: Redness and/ or swelling centered at the site of injection and one or more of the following: ➢ Swelling beyond the nearest joint ➢ Pain, redness and swelling of more than 3 days duration or ➢ Requires hospitalization Local reactions of lesser intensity may occur commonly and are generally of little consequence. For monitoring purpose, priority should be given to severe local reactions as defined above.
Central Nervous System Adverse Events
a. **Vaccine-Derived Paralytic Poliomyelitis:** Acute onset of flaccid paralysis within 4-30 days of receipt of oral polio virus vaccine (OPV), or within 4-75 days after contact with a vaccine recipient, with neurological deficits remaining 60 days after onset or death.
b. **Guillain barre Syndrome (GBS):** Acute onset of rapidly progressive, ascending, symmetrical flaccid paralysis, without fever at onset of paralysis and with sensory loss. Cases are diagnosed by cerebrospinal fluid (CSF) investigation showing dissociation between cellular count and protein content. GBS occurring with 30 days after immunization should be reported.
c. **Encephalopathy:** Encephalopathy is an acute onset of major illness temporally linked with immunization and characterized by any two of the following three conditions. ➢ Seizures; ➢ Severe alternation in level of consciousness lasting for one day or more; and ➢ Distinct change in behavior lasting one day or more. Cases occurring within 72 hours after vaccination should be reported.

d. **Encephalitis:** Encephalitis is characterized by the above mentioned symptoms and signs of cerebral inflammation and, in many cases, CSF pleocytosis and /or virus isolation. Any encephalitis occurring within 1-4 weeks following immunization should be reported.

e. **Meningitis:** Acute onset of major illness with fever, neck stiffness/positive meningeal signs (Kerning, Brudzinski). Symptoms may be subtle to similar to those of encephalitis. CSF examination is the most important diagnostic measure. CSF pleocytosis and/ or detection of microorganism (Gram stain or isolation).

f. **Seizures:** Seizures lasting from several minutes to more than 15 minutes and not accompanied by focal neurological signs or symptoms. Febrile seizures or afebrile seizures.

Other Adverse Events Requiring Investigation

Anaphylactic shock: Circulatory failure (e.g. alteration of the level of consciousness, low arterial blood pressure, weakness or absence of peripheral pulses, cold extremities secondary to reduced peripheral circulation, flushed face and increased perspiration) with or without bronchospasm and / or laryngospasm/laryngeal oedema leading to respiratory distress occurring immediately after immunization.

Persistent screaming: Inconsolable continuous crying lasting at least 3 hours accompanied by high-pitched screaming

Hypotensive-hyporesponsive episode (shock collapse): Sudden onset of pallor or cyanosis, decreased level or loss of responsiveness, decreased level of muscle tone (occurring within 48 hours of vaccination). The episode is transient and self limiting.

Osteitis / ostemyelitis: Inflammation of the bone either due to BCG immunization (occurring within 8 to 16 months after immunization) or caused by other bacterial infection.

Toxic- shock syndrome: Abrupt onset of fever, vomiting and watery diarrhea within a few hours of immunization, often leading to death within 24-48 hours.

Adverse Events not requiring investigation

Allergic reaction: Characterized by one or more of the following (1) skin manifestations (e.g. hives, eczema); (2) wheezing; (3) facial or generalized oedema.

Arthralgia : Joint pain usually including the small peripheral joints.

- Persistent: Joint pain lasting longer than 10 days
- Transient: Joint pain lasting up to approximately 10 days.

High fever (>39 C^0 / 102^{0}F): The Endogenous elevation of at least one measured body temperature >39 C/102 F

Nodule at the injection site: Presence of a discrete or well demarcated firm soft tissue mass or lump at the injection site that is sometimes referred to as a subcutaneous nodule, antigen cyst or granuloma, in the absence of abscess formation, erythema and warmth**.**

3.2 Role and Responsibilities of key players

The AEFI surveillance system involves a network of key health professionals listed below at each level of health facilities where immunization service is provided.

Health Workers/Nurses involved in immunization

- Inquiries should be made from each recipient or parent/guardian of the recipient regarding any AEFIs experienced after previous vaccination at immunization.
- Should provide a list of children vaccinated in session to the VHWs if immunization is conducted in ORC and BHU and request them to be alert, follow up and report AEFIs if any.
- Should report any serious suspected AEFI using AEFI notification from the Immunization site /BHU/hospitals to the DHO
- Should provide immediate first aid and refer AEFI to the nearest higher level health center for prompt treatment.
- Should report AEFI details in the monthly AEFI surveillance report form. A zero report should be submitted in case no AEFI is observed. Copy of AEFI cases notified and monthly AEFI surveillance report should be filed in respective health centers.
- Whenever an opportunity is available, make aware and educate the community regarding AEFIs.

Clinicians (Specialist/Chief Medical Officer/Medical Officer)

- Should ensure that the notified adverse events detected and reported are verified and have valid diagnosis as per the cases definition.
- Should investigate AEFI cases or death within 24-48 hours of notification using AEFI cases investigation form.
- Submit investigation report to DHO and programme after investigation is completed.
- Should manage AEFI and refer if required to referral hospital.
- Should present AEFI investigation to district and national AEFI committee.
- Should train field staff involved in AEFI surveillance and good quality immunization practices.

- Should provide guidance and adequate training to the field health staff on whenever necessary staff should be re-trained.
- Should encourage the staff to report AEFIs.
- Should coordinate appropriate samples collection and referral for testing with Laboratory Request Form and other documents (as outlined Annexure 1)
- Should assist the national AEFI Committee in case of AEFI investigation from national level.
- Should ensure availability of emergency drugs and medical equipment to deal with an adverse event in hospital.
- Should regularly check the emergency kits (functional status of equipment and expiry of drugs)
- Communicate and share the results of investigation with health workers and the community wherever warranted.
- Whenever an opportunity is available, sensitize and educate the community regarding AEFIs.

District Health Officer

- Should establish a functional district AEFI committee with defined Terms of Reference (ToR).
- Should ensure adequate documentation of AEFI surveillance maintained and available at respective district health centers.
- Should ensure availability of adequate AEFI registry, case notification, cases investigation form, death investigation form in all the district health centers as required by surveillance system.
- Should ensure AEFI guidelines are disseminated and available in all health centers
- Should ensure all relevant staff are trained and re-trained periodically on AEFI surveillance.
- Should identify nodal persons in BHU/hospitals for AEFI case registry and notification.
- Should notify and submit AEFI cases notification form submitted by health centers

to the programme.

- Should collate monthly AEFI surveillance reports from health centers and submit to the programme by the first week of the following month.
- Convene a meeting of the district AEFI committee if required for AEFI cases or death investigation.
- Should submit AEFI case investigation report to programme within 48 hours of notification.
- Should ensure timely management of cases and referral in consultation with CMO/MO.
- Should ensure availability of emergency drugs and medical equipment to deal with an adverse event in health centers.
- Should regularly check the emergency kits (functional status of equipment and expiry of drugs)
- Ensure adequate supervision and monitoring in health centers

Programme managers/Officers of Vaccine Preventable Disease Programme

- Should ensure a functional national AEFI committee with defined Terms of Reference.
- Maintain AEFI surveillance data at the national level.
- Analyze AEFIs surveillance data
- Share AEFI surveillance feedback to health centers and other relevant stakeholders quarterly.
- Ensure the national AEFI guidelines and reporting forms are disseminated adequately to districts.
- Assist in responding to AEFI investigation and support the dzongkhag AEFI committees in investigation when requested.
- Encourage AEFI reporting from all health centers including military hospitals
- Ensure effective AEFI monitoring and supportive supervision to districts
- Monitor reported AEFI data for potential signals of previously unrecognized signals and vaccine related adverse events and make recommendations for further investigation.

- Provide feedback of observations and recommendations of the national AEFI committee to DHO, health centers and other relevant stakeholders.
- Assist DHO on specimen collection, shipment and other support if requested for case Investigation.
- Convene the National AEFI Committee (NCIP) meeting to decide on the gravity of the AEFI case and to take decision and recommend further course of action.
- Coordination with relevant stakeholders to deal with sample referral and testing or other procedures pertaining to AEFI investigation.
- Ensure that the communication plan is activated to handle any crisis
- Engage the national AEFI committee timely for final conclusion (causality investigation) on AEFI investigated cases.
- Share report of casualty assessment and recommendation emerged from the national AEFI committee to the Ministry of Health and other relevant stakeholders including media if required.

National AEFI Committee

The relevant experts (Epidemiologist / Public Health Specialist, Pediatrician, Medical specialist, Microbiologist, Neurologist, Pathologist, Forensic expert, Pharmacist and representatives from DRA should constitute as members of the AEFI committee. Representatives from partner agencies can be on panel as ad hoc members and representatives should be invited when required. Programme manager of the programme should be the member secretary.

ToR of National AEFI committee

- Analyze the case investigation reporting forms and plan for investigation of the AEFI as a team.
- Monitor the timely submission of completed investigation forms along with supporting documents/medical record etc
- Prepare a case investigation report.
- Analyze and review the quarterly AEFI data for any programmatic errors and remedial measures for the same.
- Conduct in casualty assessment.
- Monitor and analyze non serious AEFI data every quarter.
- Support the spokesperson for media communication.

- Where needed facilitates in propagating the message of reporting AEFI from all sectors (including private sector).
- Communicate and share the conclusions and results of investigation with health workers and the community where warranted.
- Any other responsibility in context to vaccine safety that the committee would like to add.

Drug Regulatory Authority

AEFI surveillance is an important functional component of the NRA (National Regulatory authority) not only for assurance of vaccine quality in the country but also for prequalification of vaccines. Core functions of the NRA are:

- Marketing authorization and licensing activities,
- Post-marketing surveillance including surveillance for Adverse Events Following Immunization (AEFI)
- Control and release each batch of vaccine individually, including recalling if necessary (NRA)
- Coordination of Lot release process,
- Laboratory support,
- Regulatory inspections of Good Manufacturing Practices (GMP)
- Authorization and approval of clinical trials of vaccine.
- Evaluate and monitor vaccine performance including safety
- Consider the vaccine safety profile of all vaccines at registration and seek advice from DTAC as and when required.

Drug Testing Laboratory

The Drug Testing Laboratory under the Public Health Laboratory is a National Control Laboratory (NCL).

- Should assist causality assessment of deaths and unusual events conducted by programme.

- Should receive vaccine samples or initiate collection of samples in coordination with DRA
- Should Identify reference laboratories in coordination with WHO on biological samples and vaccine quality testing

4. AEFI REPROTING

All medical events should be reported if temporally related to immunization including events occurring within 30 days following administration of a vaccine unless otherwise specified. The events that are known to be identified as AEFI (case definitions are given in Annexure 1), and also events which occur in clusters or cause major public concern should be reported using Adverse Events Following Immunization notification for (AEFI Form 1).

Any unexplained sudden death of a vaccine recipient temporally linked (**within 30 days**) to immunization, where no other clear cause of death can be established should be reported. In addition, any unusual events should be reported. As soon as health staff detect any AEFI, it is important to ensure that the recipient has received necessary health care including treatment if it is indicated before reporting and reassure the affected recipient/ parents/guardian that an investigation would be carried out**.** The health workers should then fill up the AEFI notification form and send it to the DHO by the fastest means possible.

On receiving AEFI notification from the field, the DHO should coordinate with specialist/CMO/MO to verify the information and confirm AEFI reports. Case should be then reported to the programme immediately.

4.1 Routine Immunization programme

An immunization service is mainly provided in the government health centers. However, the private sector may also provide immunization service soon.

In health centers, immunization is provided at OutReach Clinic on fixed days at least once a month, at BHU’s once a week, at Community Health Unit of the district or referral hospitals once a week or on daily basis. It is therefore important that all levels providing immunizations are sensitized to detect, investigate and report AEFIs. Each health center should identify a focal person to coordinate reporting.

District Health Office (DHO) shall be the nodal person at the district to monitor the AEFI reporting from their respective BHUs and hospitals and coordinate investigation. DHO should also be responsible for reporting to the programme (VPDP).

In regional and national referral hospitals including urban health centers, focal persons identified should monitor the AEFI reporting and coordinate investigation. The focal point will also be responsible to report to the programme (VPDP).

4.2 Mass Immunization / Special immunization Programme

It is of utmost importance to report all AEFI to VPDP in an event of mass immunization or special immunization programme for 2 reasons:

i. Mass Immunization and special immunization programmes cover a large number of individuals in a particular target group in a specified given time period and therefore, an excess number of adverse events may be reported within a short time period. Unless these are not properly investigated or analyzed, it can cause undue concern among the public and may affect the immunization programme.

ii. During special immunization programmes, a new vaccine may be introduced with no prior experience or with little information on adverse reactions. There is a possibility of detecting signals through strengthening surveillance during such special immunization programmes.

4.3 How can reporting be encouraged?

Health workers should be encouraged to report adverse events without fear or penalty. Available AEFIs should be reported even if there is a delay in the submission of information by the field staff. It is important that health worker staff should be given feedback about the results of investigations and action taken. This has to be carried out at each level of the surveillance process and should include positive feedback such as an acknowledgement for reports received. Feedback also should include sharing information on management of child/recipient especially concerning future vaccination and the outcome of investigations or causality assessment when these are carried out.

5. AEFI INVESTIGATION

The goal of the AEFI investigation is to find the cause of an AEFI. If the cause is identified as a programme error, remedial action can be taken promptly and the public can be assured of the integrity of the immunization services. Even if the cause cannot be identified or the cause of the event was attributed to some other reason, the fact that health centers investigated the incident itself will increase public confidence towards immunization.

Purpose of investigating AEFI cases are:

1. To confirm the reported diagnosis or establish other possible diagnosis
2. To identify details of specifications of the vaccine used to immunize the affected recipient and any vaccine related link for the given AEFI
3. To examine the operational aspects of the programme.
4. To determine whether a reported event was a single incident or one of a cluster and find out vaccine used vaccines used.
5. To determine whether unimmunized people are experiencing the same medical incidents.

5.1 Basis of AEFI Investigation

There are many background factors / reasons involved in deciding whether an adverse event is actually caused by the vaccine. Vaccinations are carried out at an age when any underlying diseases become evident among children. The fact that the vaccine was administered within a reasonable time period of occurrence of signs and symptoms of a disease does not automatically suggest that the vaccine is the cause or aggravating or contributing factor. Systematic assessment of the patient and the relevant factors will determine the cause and effect relationship of the event.

The basis of investigation is to identify whether the;

i. Adverse events are not related to the vaccine and vaccination.
ii. Adverse events are related to the vaccination; operational aspect of the programme.
iii. Adverse Events are related to the vaccine.

5.1.1 Adverse event is not related to the vaccine and vaccination

Some of the events may just coincide with the vaccine/vaccination; for instance, the event might have occurred even if the person had not received the vaccine. Occurrence of the event on a coincidental basis could be demonstrated if the same event also occurred in the unimmunized group in the population.

The factors which need to be considered

- Whether several cases occurred in the same clinic.
- Whether the unimmunized population of the same age group presented with the same symptoms/events.
- Whether other recipients vaccinated with the same batch of vaccine presented with the same symptoms/events.

5.1.2 Adverse event is related to the vaccination; operational aspect of the programme

Table 7: Adverse event is related to programmatic errors

Related to vaccine, diluents & administration	Related to Needles & Syringes
Incorrect dosage of vaccine and/or diluent	Unsafe use of needle and disposable syringe
Reconstitution of the vaccine with wrong diluents	Reuse of 5 ml reconstitution (diluents) syringe
Improper preparation of vaccines	Improper handling of the syringes and needles
Incorrect method of administration	Improper storage of the syringes and needles
Substitution of vaccines or diluents with drugs or other substances	Syringes & needles used after their expiry date
Contamination of vaccines or diluents	Failure to verify the condition of the packaging that guarantees the sterility of needles and syringes
Improper storage of the vaccines	
Vaccines and diluents used after their expiration date	
Vaccines not discarded at the end of immunization session and used at a subsequent one	
Ignoring contradiction to vaccination e.g. child who had a severe reaction with a previous dose of DPT vaccine immunized with the same vaccine again.	

5.1.3 Adverse events related to the vaccine

These are due to the inherent properties of the vaccine antigen or excipients (Adjuvant, preservatives, stabilizer, antibiotics or any other component). Minor events usually settle with

treatment and have no long term consequences. However, serious events, although very rare, require thorough investigation where the quality of the vaccine is suspected to be the cause.

The factors to be considered during investigation of such cases;

- Frequency of occurrence (common/rare/not previously reported)-whether the events occur within the expected frequency range.
- Known reaction to the vaccine.
- Similar events reported among the un-immunized population.
- Event caused by the plausible mechanism due to biological properties of the vaccine.
- Significant temporal relationship of the event and the immunization.
- Past history of similar events; related or independent of vaccination.
- History of drug therapy; concomitant/previous.
- Concomitant or preceding medical condition which could explain the event e.g immune-compromised status of the recipient.
- Any other factors that could explain the event; e.g. programme errors.

If the event is serious, unexpected vaccine reaction or occurred with unexpected frequency;

- Contact DHO and VPDP immediately
- Vaccine suspension or withdrawal at district or national level would be done only on recommendation of national AEFI expert committee and relevant stakeholder.
- Re-evaluate the quality of the vaccine with the DRA (National Regulatory Authority) communicating with the manufacturer, if necessary.
- Report findings of the investigation to the health staff and community.

If causality cannot be determined, the reasons need to be indicated to the concerned clinicians and health workers.

5.2 What adverse events to investigate?

Events to be investigated are:

- AEFIs that are life threatening or those that result in hospitalization (or prolong hospitalization), disability (or have the potential to result in disability) or death.
- AEFIs that may have been caused by programme error and occur in cluster (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome).

- Serious events of unexplained cause occurring within 30 days after a vaccination
- Events causing significant parental or community concern.
- Events in which vaccine quality is suspected
- All injection site abscesses
- All cases of BCG lymphadenitis

5.3 When should an investigation take place?

Investigation should be urgently conducted following notification if deemed necessary so that the cause may be determined (where possible) and in some events additional cases are prevented.

5.4 How should an investigation take place?

All serious AEFI should be investigated by the field investigation team. In case of death a pediatrician should be included in the team recommended by the National AEFI Committee. After an investigation, the concerned team should present findings to the national AEFI committee.

In cases of minor AEFIs, the reporting health workers should conduct the investigation. However, an investigation report should be sent to DHO. The copy of the verified report should be sent to the programme by DHO.

If the event is of national health and public concern, a team from the national AFEI committee should conduct the investigation.

Team Composition

The national investigation team should comprise following experts and some National AEFI committee members can be the team members:

- Epidemiologist
- Clinician as per suspected vaccine (Obs-Gyn, Physician, Pediatrician, Forensic Pathologist)
- NRA member, if necessary
- EPI Personnel
- Provincial/ District EPI or Health managers

District investigation team should include:

- Doctor (In case of death preferably a pediatrician should be involved from the nearest RRH)
- District Health Officer/ADHO
- MCH In-charge

Preparation and Planning for Investigation

Investigation will be coordinated by the national program. Program will be responsible for the following:

1. Providing overview of EPI program (by EPI manager) including the following: EPI Schedule, Health and EPI structure, birth cohort and coverage, Cold Chain and Logistics structure, overall demand and trust in program, media and sharing of relevant documents and baseline data
2. Reviewing Notification Form and any other data
3. Collecting information from National Stakeholders (Form 1)
4. Briefing team about national stakeholders, planned visit sites and persons to meet during visit
5. Informing counterparts at district and health facility about planned investigation visit
6. Equipping team with requisite investigation forms
7. Assigning role and responsibilities for specific aspects of the investigation (by EPI manager who is the focal point
8. Communicating with media through designated spokesperson of the AEFI committee about current stage of investigation and any relevant preliminary findings

5.5 Conducting the investigation:

- Introduce team to district health officials and inform them of the objectives of the investigation and planned activities
- Collect relevant district/health facility data and compare with national data
- Simultaneously conduct investigations as per assigned tasks
- Case investigation should be done using AEFI case investigation form (Annexure 6)
- Case investigation should be completed within 48 hours of case notification.

Following information should be obtained during the investigation:

- Inquire from the patient (if possible)/parents about the health condition of the patient
- Check about the vaccine that is attributed and other drugs received
- Inquire about other vaccines received
- Question about the quality of immunization services

- Observe the immunization sessions in action
- Inquire about similar events in unvaccinated persons
- Support case definition or establish a more specific case definition if needed
- Seek information from other recipients/community regarding any similar events
- If appropriate, the implicated vaccine, logistic samples, CSF, Serum (or other biological products) should be collected and dispatched to the laboratory with the Laboratory Requisition Form for testing and further analysis (See Annexure 1).

1. Completed Case investigation form should be sent to the programme not later than 7 days of submission of case notification form.
2. After receiving the case investigation form, the programme should be assigned Epi number [*BHU (AEFI) – indicates country and AEFI, follow by district code (use three alphabets), year (use last two digit and cases number in two decimal place. Example: BHU (AEFI)-PAR-14-01 – 1st AEFI cases from Paro investigated in 2014*) and
3. Submit AEFI cases to the national AEFI committee for causality assessment.
4. Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine and diluent may be tested for safety, sterility and chemical composition and the needles and syringes for sterility. Testing should only be requested on a clear suspicion and not as a routine procedure.

5.6 Death Investigation:

In the event of a death following immunization, it should be notified to the programme and the field investigation has to be initiated promptly by the district AEFI team with the help of the national AEFI committee.

Following information should be obtained during the investigation and format for investigation of death following immunization has to be completed (Annex 7).

a. Detailed history from the parents/guardian
   - Pre immunization health status.
   - Sequelae of the AEFI following immunization (Since details of the immediate events leading to death bears great importance in the causality assessment preferably this information has to be obtained by a medical personnel with a sound paediatric knowledge).
   - Significant past medical problems of the child.

b. Details of all medical interventions (case history) has to be obtained including laboratory investigation reports and preserved for subsequent causality assessment.
c. Information on storage conditions, maintenance of cold chain and handling of vaccines, diluents and syringes.
d. Information on similar events among other recipients of vaccines in the same health center and the district.
e. Where applicable and possible, a post mortem examination should be conducted for all deaths suspected to have been caused by vaccine/immunization. It should be performed by a qualified medical officer in legal medicine.

5.7 Investigation of AEFI cluster

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. Exact nature of the relationship between the adverse events (e.g. duration of time, proximity of place); will differ by nature of events and the circumstances in which they occur. Investigation of a cluster should follow the same principles (figure 2) with following steps:

- Establishment of a case definition, if there is no case definition laid down previously.
- Identification of all immunized and unimmunized populations who meet the case definition.
- Obtaining immunization history (when, where and which vaccines were given).
- Identification of any other common exposures of the cases.

If all cases receive vaccines from the same health worker/ immunization clinic and there are no other cases – **Immunization related error is likely.**

If all cases received the same vaccine or lot from the different clinics and there are no similar cases in the general community, a problem with the vaccine is likely – **vaccine defect.**

If the event is a known vaccine reaction but occurring at an increased rate – **an immunization related error or a vaccine defect are likely causes.**

If cases include people in the same area in the same age group who were not immunized – **event was probably coincidental**.

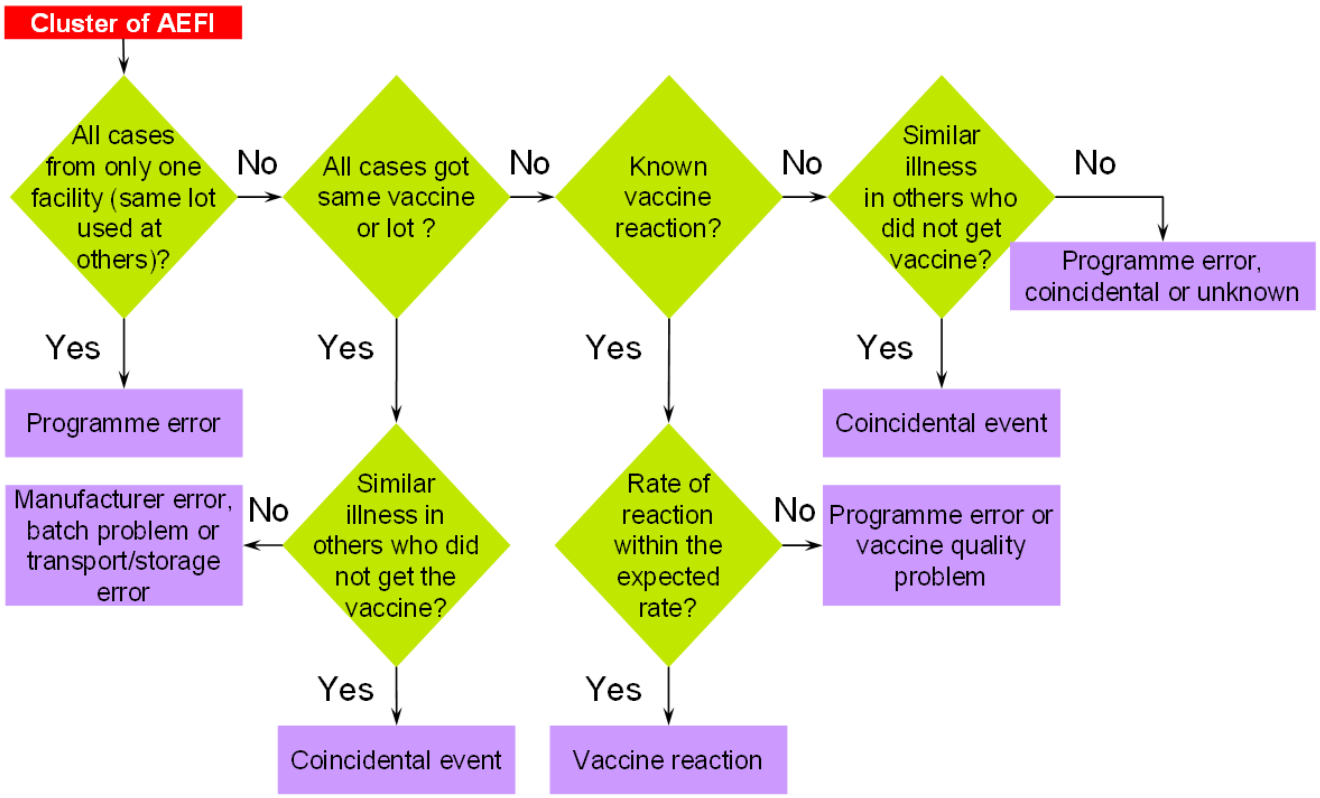


Figure 2: Identifying cause in an AEFI cluster

6. ANAYSIS OF AEFI DATA

Analysis of AEFI surveillance data consists of following components:

- Completeness of AEFI forms received.
- Identifying health centers where AEFIs are not reported.
- Determine whether it is due to failure of reporting or whether there are no AEFIs to be reported. Check on “zero reporting”.
- Assessing AEFI reports received during stipulated time period
- Assessing number of events and calculating rate for 100,000 doses of antigen (vaccine) used.
- Categorizing the type of AEFI (by the new classification adopted in 2012)
- Analyzing immunization related error by number and rates by area and number of doses of relevant vaccines used.
- Reviewing case investigation reports of each patient.

- Reviewing other data about the event and the community, where it took place may provide important clues to, making a final diagnosis and identifying a probable cause. It may not be possible to make a diagnosis, the cause might not be evident or there might be more than one cause.

6.1 Who should analyse the data?

Data analysis should be carried out at national level by programme. All reports should be analyzed to identify the type of AEFI, particularly the programe errors. This is largely to take corrective action in a timely manner. Before the analysis, programme needs to verify data and reassure its accuracy. Analysis by health centers wise will help to identify issues and may focus on corrective action.

6.2 How should analyse the data?

Follow following step to analyze the data:

1. First diagnose the case. Information collected on the patient's signs and symptoms, the history of the event, patient's past medical history, data on suspected immunization and laboratory results all may contribute to the diagnosis. Standard case definitions should be used (Table 6).
2. Line list all reported AEFI data followed by tabulating by place (health centers and district), person and time.
3. Analyze by antigens and by type of reported adverse events (high fever, abscess). Number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year).
4. Analyze if possible AEFI rates by first or second or third dose, when the antigen is administered more than once. For this, the number of doses administered of the given antigen as first, second or third dose need to be used as the denominator.

6.3 How should a cause be determined?

For a few medical events, the diagnosis itself will show the cause whether it is programme related, vaccine induced, coincidental or injection reaction. In others, external evidence may be required to identify the cause. Later it will be possible to analyze the data and assign a 'cause' and then to further classify into one of the categories of AEFI.

Recommendations should be made on the findings and conclusions. These recommendations should include the action that should be taken to remedy the problem identified. Action should be taken by the programme managers and district health authority at the health center.

6.4 Preparation and submission of report

Preparing and sharing information to stakeholders is important in order to ensure dissemination of correct information and thereby to ensure smooth functioning of the national immunization programmme in the country. This should be done as follows:

- Compile all investigation reports from the team
- Prepare summary case investigation form
- AEFI committee to carry out Causality Assessment
- Submit Summary Report to EPI Program and DRA
- Submit press release/briefing by appointed spokesperson or media focal person if necessary
- AEFI committee to follow-up recommended actions by EPI program

All serious AEFI reported and investigated should be actively reported to WHO Post-marketing Surveillance (PMS) network, Upasala center.

7. CAUSALITY ASSESSMENT OF AEFI

Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine/s received. It is a critical part of AEFI monitoring and enhances confidence in the national immunization programme among the health sector and public. All reported AEFIs require verification of the diagnosis; coding, review, collation and storage of data; if an AEFI is serious it requires a systematic, standardized causality assessment.

Causality assessment is important for:

- Identification of urgent problems for investigation/action.
- Identification of immunization related errors and batch problems.
- Testing of hypothesis and research.
- A basis for estimation of rates of serious AEFIs.
- Comparison of AEFIs between vaccine brands.
- Pre and post marketing surveillance.

The quality of the causality assessment process depends on several factors:

1. Effectiveness of the reporting system.
2. Quality of the causality review process.

In settings where causality assessment is undertaken it is important to consider all possible explanations for an event and the degree of likelihood for each before addressing the question of whether or not a vaccine product, quality defect, the immunization process or immunization anxiety caused a given event or if it was due to something else such as an intercurrent infection. Most often because of missing or imprecise data in the AEFI report(s) resulting in a case being deemed unclassifiable.

7.1 Criteria for establishing causality

Five **criteria** by Bradford-Hill will provide a logical way to assess the association and test the hypotheses during the causality assessment.

Criteria (Evidence) for establishing Causality:

- Strength of the association
- Consistency of the association
- Specificity of the association
- Temporal sequence
- Biologic plausibility (coherence with existing information)
- Causality assessment aims to classify the likelihood of a causal association between a vaccine and an adverse event.

7.2 Causality assessment method

There are four steps in causality assessment as per 2012, WHO guideline that allows the National Committees for AEFI to review and conduct causality assessment on serious cases reported.

Step 1: Eligibility

To proceed with causality assessment, it is necessary to have a valid diagnosis for the reported AEFI as per the standard case definition. The case definitions can be adopted from standard medical literature, national guidelines or adopted locally. It is best to adopt the Brighton Collaboration case definition (https://brightoncollaboration.org/public)

Step 2: Checklist

The checklist contains questionnaires to guide the Committee to collate the evidence needed for case review. It is designed to assemble information on patient-immunization-AEFI

relationship in the following key areas as reflected in the table below: Once the checklist is systematically completed, the answers in the checklist are applied to the algorithm.

	Yes	No	Unknown
1. Is there strong evidence for other causes?	☐	☐	☐
2.Is there a known causal association with the vaccine / vaccination? a.Relationship with vaccine ingredients b.Immunization Error c.Injection Reaction	☐ ☐ ☐	☐ ☐ ☐	☐ ☐ ☐
3.Was the event within the time window of increased risk?	☐	☐	☐
4.Is there strong evidence against a causal association?	☐	☐	☐
5.Other qualifying factors	☐	☐	☐

Step 3: Algorithm

The algorithm is based on key questions given in the checklist. Stepwise approach in algorithm helps determine if the AEFI could be *consistent* or *inconsistent* with an association to immunization, *ndeterminate* or *unclassifiable*.

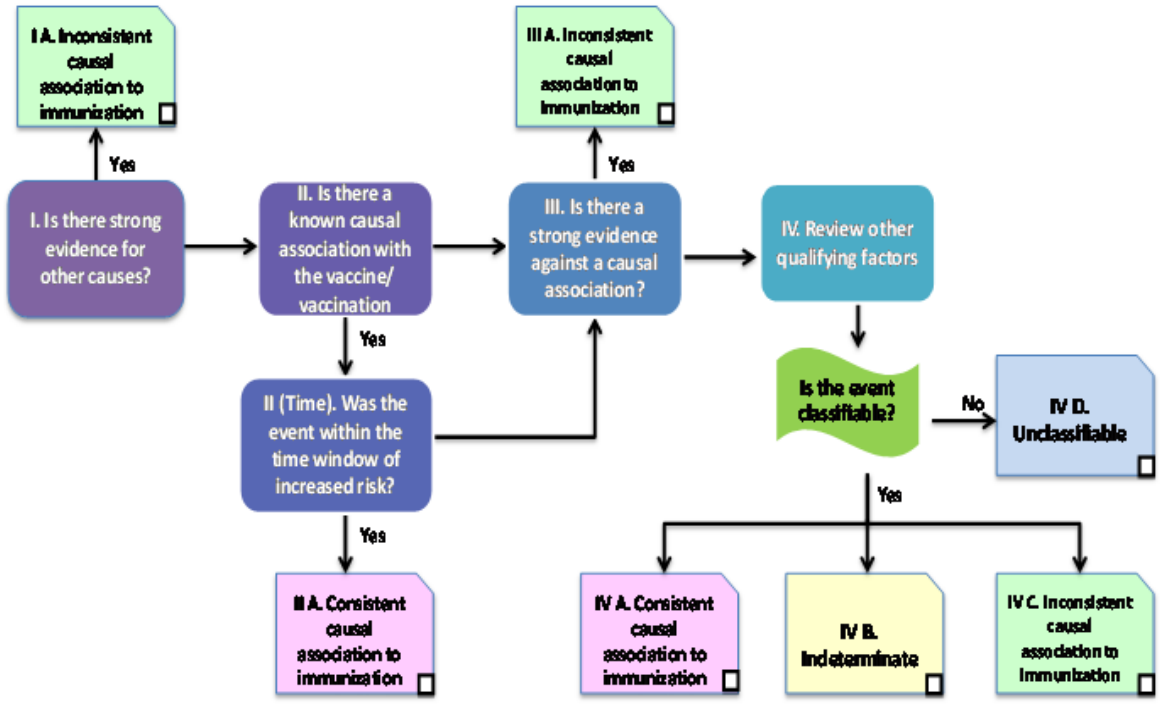


Figure 3: Algorithm to determine AEFI classification

Step 4: Classification

The final classification is based on the availability of adequate information as follows:

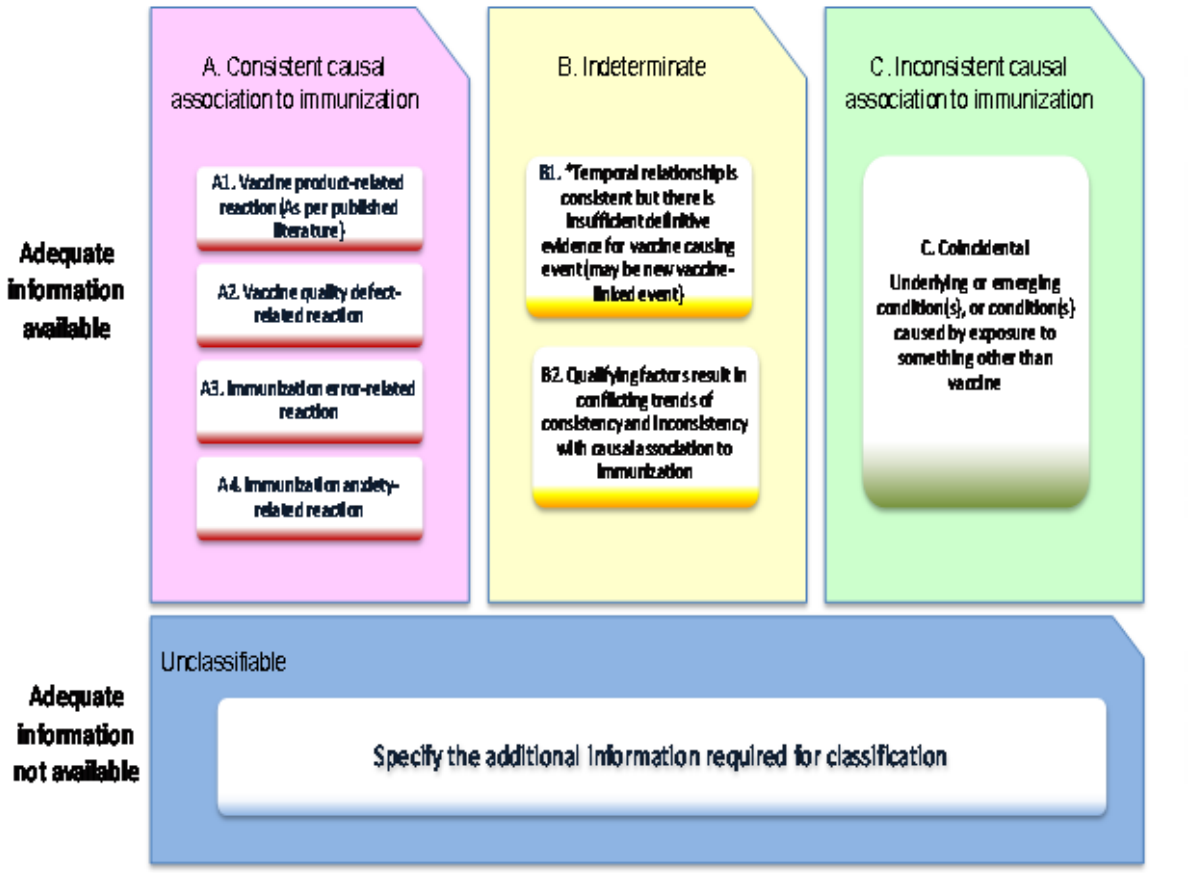


Figure 4: AEFI classification chart

8. FOLLOW UP ACTION

AEFI detection, investigation, analysis and causality assessment must lead to action if the credibility of immunization services is to remain high. These follow-up actions include diagnosis, treatment, reporting, communication and corrective actions.

8.1 Diagnosis: An Adverse Event Following Immunization (AEFI) is a medical incidence that takes place after an immunization, causes concern, and is believed to be caused by immunization. An AEFI may occur because of programmatic errors or sensitivity to vaccines or it is coincidentally. Whatever the cause, AEFIs must be taken seriously and the management must be rapid and professional.

8.2 Treatment

Treatment must be the first response to an AEFI. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by reassuring and educating parents during immunization. Health workers should also know how to identify serious AEFIs and when to refer to the relevant authorities. It is very important that all health workers be aware of the management of AEFI's especially anaphylaxis.

8.3 Corrective actions

When the investigation is completed and the cause of AEFI is identified, it could be included into the relevant category and remedial action. Table 9 illustrates some corrective action to be taken after investigating AEFI.

8.4 Training

The training on AEFI surveillance is very important to update knowledge and develop skills and confidence among the health workers. The training should be conducted periodically and regularly.

8.5 Awareness

Awareness can be done using various communication mediums to all stakeholders linked to the immunization programme such as: professionals, teachers, volunteers, policy makers, politicians and media.

Table 8: Corrective actions to be taken after investigating AEFI

Vaccine quality defects	If a higher reaction rate than expected (refer to table 2.3, page no 5) is being reported from a specific vaccine or batch then obtain information from the manufacturer and consider ● Withdrawal/temporary suspension of the suspected batch of vaccine. ● Arrange for return of implicated vaccine, if appropriate ● Change manufacturing specifications or quality control ● Replace the vaccine with a new stock of quality reassured vaccine
Immunization related errors **(Programme Errors)**	Correcting the cause of the error ● Proper maintenance of cold chain ● Intensify monitoring and supervision of health staff ● Training of field health staff ● Change faulty procedures at the immunization clinics: Whatever action is taken, it is important to review at a later

	date to check that the immunization errors have been corrected.
Coincidental	• Main task is to exclude other causes for AEFI • Communication with parents, community and field staff is crucial to impress that the cause and effect relationship is just coincidental • Patient should be referred to a doctor if the medical condition warrants treatment and medical care.
Injection Reaction	• This is due to the anxiety and fear of injection, which is usually common during school immunization programmes • Effective communication with children and caregivers to relieve their anxiety is important
Unknown /Undetermined	• Depending on the nature of the event, its extent and whether it is ongoing, further technical assistance from AEFI committee will be needed to assist the investigation and causal assessment • If necessary a special study needs to be conducted (to study possible signals)

8.6 Communication /Sharing AEFI information with Media

Media plays an important role in disseminating information and in developing public awareness. Use of media for the benefit of an immunization programme is necessary. Therefore, AEFI data may be shared with the media, when it is deemed necessary. However, sharing AEFI information with the media is the responsibility of the Ministry of Health. According to the Ministry regulation, sharing any information with the media should be done only with prior approval from the Ministry.

8.7 Media Management when an AEFI has occurred

Every single AEFI must be investigated in detail to establish cause and effect since the media would report to the public which could derail immunization service. Therefore, preliminary correct information must be available with programme to share with media if required and media must be managed with utmost sensitive and caution.

8.7.1 Monitor-media:

When an AEFI occurs, substantive inaccuracies can get reported; for example, regarding the number of AEFI cases, gravity of the case, allegations of negligence, or simple rumors about vaccine procurement. The AEFI Committee should move very quickly to correct them, because the longer misinformation remains in the information environment, the more difficult it becomes to correct. The AEFI Committee could take the following immediate actions:

- Analyze rumor, its level, and potential to cause damage.

- Anticipate how situations might evolve following response; prepare before responding.
- Deal with a simple mistake with a simple solution. If it is an isolated error, make a polite call to the reporter and offer to help the reporter with correct data and facts then and in the future.
- If the rumor is confined to a small audience, correct it within that group only. If the error is widely reported, you may call a media conference to present the correct facts before it leads to further damage or proves detrimental to the programme goals.
- Plan how to prevent future rumors.

8.6.2 Prepare messages:

The best messages get to the heart of the problem without lengthy explanations. Listeners and viewers remember that one key message if they remember nothing else. Try to repeat the message at least once during an interview with the media. For instance, here are two effective messages on immunization in general:

- Immunization is the most cost-effective health intervention.
- Immunization is the right of every child.

Some more examples of messaging specific to the situation

- Benefit of immunization in preventing disease is well proven.
- It is very risky not to immunize (risk of disease and complications).
- Before the introduction of vaccines, vaccine-preventable diseases caused millions of deaths and/or disabilities. That situation would return without continued use of vaccines.
- Vaccines do cause some reactions, but these are rarely serious and hardly ever cause long-term problems (have data ready and available to substantiate this fact).
- We have well-established immunization safety surveillance in place. Immunization safety is of paramount importance, and even the slightest suspicion of a problem is investigated.
- 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.

8.6.3 Prepare a media release:

An effective media release should include:

- A complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI, or coincidental event).
- The media release must specifically answer the '6 Ws' (***Who*** *is affected/is responsible?,* ***What*** *has happened? What is being done?,* ***Where*** *has it happened?,* ***When*** *did it happen?,* ***Why*** *did it happen?,* ***Will*** *it happen again*?).
- Keep media releases free from technical jargon.
- An outline of actions taken or planned (such as the AEFI investigation).
- A description of the cause of the event (but only when this is known with certainty).
- An assurance that corrective action has been taken or will be taken.
- Reference to any relevant publication, video material or web site.
- Spokesperson's details.
- Limited to one page of matter (400-500 words max).
- Short sentences (not exceeding two lines).
- Key message(s) are repeated.

8. FEEDBACK AND MONITORING

Making the regular feedback (quarterly and annually report) available to health workers and relevant stakeholders will encourage their participation and support and provide positive feedback for their reporting.

Feedback should include:

- Number of AEFI reports, categorized by type of reaction and vaccine(s) and causality assessment (with denominator data on number of doses of vaccine given)
- Rate of each adverse event by vaccine (and lot number) nationally and by region
- Unusual or unusually severe events or large clusters
- Summary of other important/unusual investigations

The AEFI surveillance system should be regularly reviewed at all levels to ensure that the system is effective. Some of the key indicators that would help to monitor the system are Timeliness, completeness and accuracy of AEFI reporting.

- Percentage of AEFI cases reported in time
- Percentage of AEFI case notification form completed
- Percentage AEFI cases investigated within 48 hours of case notification and report to programme.
- Percentage of AEFI case investigation form completed
- Percentage of Causality Assessment completed for AEFI cases investigated and reported to programme within 90 days of submission of case.

REFERENCE:

1. Adverse Events following Immunization surveillance and response operational guideline, Editions 1, 2011
2. National guideline on Immunization safety surveillance, Epidemiology Unit, Ministry of Health, Sri Lanka, 2012
3. Causality Assessment of an adverse event following immunization (AEFI), User manual for revised WHO classification WHO/HIS/EMP/QSS. March 2013

Annexure 1:

Laboratory Aspects of AEFI

Laboratory testing of samples is not mandatory following AEFI particularly if the cause is evident such as a coincidental event or a program error. As required for the investigation, appropriate specimens in the correct quantity should be collected. Laboratory specimens should be accompanied by clear supporting documents, reasons for specimen collection and any additional information required by the investigators.

Table 8: Activities and responsibilities for specimen collection

	Activity	Responsibility
1	Decision to collect sample (samples should be collected as soon as possible and sent only if the National AEFI committee decides)	• Dzongkhag AEFI committee and DRA drug inspector.
2	Decision to temporarily suspend the use of implicated batch of the vaccine/diluent/logistics	• NCIP and MoH • DRA.
3	Collection and sending of samples	• The Drug Inspector & PHL
4	Decision on type of samples that need to be collected	• Based on recommendations of the National AEFI committee. • The Drug Inspector may also collect additional samples as per the requirement of the PHL.
5	Packaging & Cold Chain of samples	• Drug Inspector and PHL
6	Sealing of specimen using "official lac seal"	• DRA,Drug Inspector;
7	Transportation of samples to laboratories	• DHO /Drug inspector
8	Laboratory for sending specimen	• PHL and PHL Identified laboratories.
9	Funding	• DoPH, MoH and DRA
10	Reporting and sharing of laboratory results/ reports	• The laboratory as a rule will forward a copy of the report to DRA and MoH,

1. **Testing of Biological samples**

PHL with the support from WHO should identify reliable reference laboratories for testing of biological products like blood, CSF, urine if require for further analysis.

1.1 **Specimens collection**

It is difficult to generalize what specimens will be required in a given situation as it will depend on the symptoms and signs of the patient and the clinical decisions made by the doctor in charge of the case. Table 9 gives a general outline of some of the specimens that could be collected. The list is not exhaustive.

Table 9: Biological specimens to be collected for testing

Event	Specimen from the patient
Severe Local Reaction Abscess Lymphadenitis	 Swab , Blood Blood
CNS Adverse events CNS Symptoms, No paralysis CNS Symptoms, with paralysis	 Cerebrospinal fluid (CSF), blood Stool *
Other Anaphylaxis Toxic Shock Syndrome Death	 Blood, Blood culture, Post mortem tissue specimen (as directed by physician)

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

2. **Testing of vaccine/ diluents by National Drug Testing Laboratory, PHL**

On the receipt of adequate samples with proper and complete documentation, DTL shall in coordination with DRA, WHO identify laboratory for testing of vaccines and diluents for physical aspects, sterility, abnormal toxicity and biochemical identity. Tests for potency are not applicable in AEFI cases (it is related to efficacy rather than safety of vaccines). The laboratory tests performed by the identified laboratory will dispatch results to the DTL in approximately 30-45 days from the date of receipt of samples from DTL. The DTL shall officially submit the test result to DRA and MoH.

2.1 Vaccine sample collection

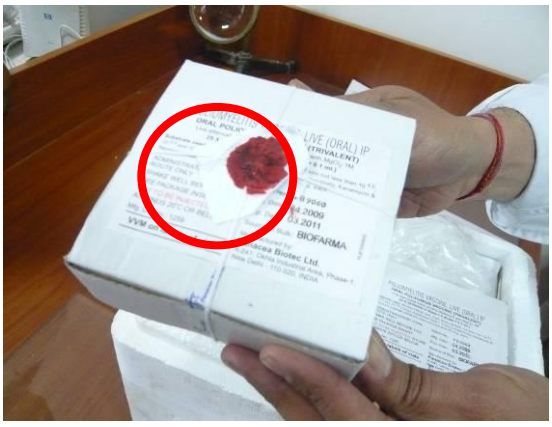
The Drug inspector/ DHO should be involved in the collection of adequate quantity of

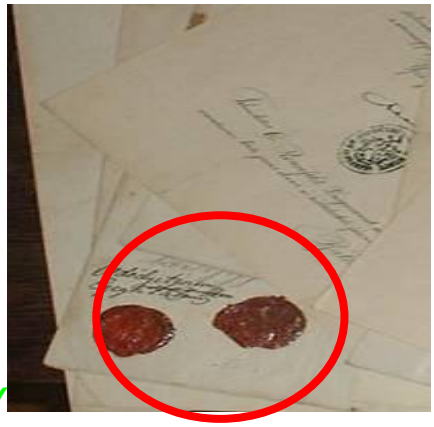
implicated vaccine/ diluent samples from the site of occurrence of AEFI and last vaccine storage point and shipping the same in cold chain to the PHL as early as possible.

- First collect each vaccine / diluent as described in table 5.2. Prepare four sealed sets with equal quantity and
  - Send 1 set to PHL.
  - Retain 1 set at the site of collection (BHU/DH or EPI regional store).
  - Retain 2 sets with the drug inspector DRA.
- The desired quantity of vaccines or diluents must be collected from the next available vaccine storage point if the numbers outlined in table 5.2 are not available at the last vaccine storage point.
- It is important that the quantity required by the PHL must not be compromised.

2.2 Packing of samples

- Separate plastic zipper bags should be used for packing different vaccine and diluents.
- The name, age, date of collection, AEFI epid number and point of collection of vaccines/ diluents should be mentioned only on the label of each plastic zipper bag.
- All the packed zipper bags (separate for vaccines and diluents) should then be put in a bigger zipper bag.
- The big zipper bag should be placed in a card board box, tied with a string from all sides and an “official lac seal” affixed by the drug inspector (Fig 8 and 10).





1.3 **Documentation and transportation of sample to laboratory**

- The completed LRF (Annex 4) also sealed with the same “official lac seal” should accompany the samples sent to the laboratory. The “official lac seal” ensures that the samples and details sent to laboratory are not tempered / changed during transportation.

- Ensure that the completed investigation forms also accompany the samples to the laboratory.
- Vaccines and diluents are tested simultaneously, therefore freeze dried vaccines (BCG, Measles, and JE) should be accompanied by their respective diluents.
- The sample should be transported to the laboratory under cold chain (vaccine carrier with ice packs or thermocol boxes with icepacks) preferably through a messenger.
- PHL accepts samples received on all days of the week. The concern offical carrying the samples to PHL must insist on getting the 'sample received receipt' for official record. This receipt will also provide details on the condition of samples received in the laboratory.
- Samples may also be sent by courier that has experience in handling biological products and can also **guarantee** delivery up to PHL within the stipulated time under the stipulated conditions.

Table 10: Quantity of implicated vaccine / diluents to be collected

Vaccine	**Quantity to be collected**		**Quantity to be shipped to PHL for referring of samples for testing**	
	Unused vaccine vials / ampoule (A)	Unused diluent vials/ ampoule (B)	Unused vaccine vials/ ampoules (one fourth of total samples collected) (C)	Unused diluent vials/ ampoule (one fourth of total samples collected) (D)
DPT group of vaccines (including Pentavalent)	10 dose X 40 vials	NA	10 dose X 10 vials	NA
	OR 01 dose X 120 vials	NA	OR 01 dose X 30 vials	NA
BCG Vaccine	10 dose X 160 vials	160 diluents	10 dose X 40 vials	40 diluents
	20 dose X 160 vials	160 diluents	20 dose X 40 vials	40 diluents
Oral Polio Vaccines	20 dose X 40 vials	NA	20 dose X 10 vials	NA
Measles/MMR Group	01 dose X 80 vials	80 diluents	01 dose X 20 vials	20 diluents
	OR 05 dose X 60 vials	60 diluents	OR 05 dose X 15 vials	15 diluents
	OR 10 dose X 40 vials	40 diluents	OR 10 dose X 10 vials	10 diluents

JE & Hepatitis vaccines	01 dose X 120 vials	120 diluents	01 dose X 30 vials	30 diluents
	OR 05 dose X 60 vials	60 diluents	OR 05 dose X 15 vials	15 diluents
	OR 10 dose X 40 vials	40 diluents	OR 10 dose X 10 vials	10 diluents

Example of vaccine / diluent collection

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

As per guidelines (Table 8) the team comprising DHO and Drug inspector planned to collect 60 vials of Measles vaccine and 60 ampoules of measles diluent.

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

The next step was to collect 60 measles diluents; they could only collect 45 diluents of the implicated batch from BHU and another 15 diluents from the EPI vaccine store. The total quantity required (i.e. 60 diluents) was now complete. The sample was packed in zipper bag and labeled accordingly.

The zipped and labeled bunches of 15 vaccines and 15 diluents were placed in cardboard cartons and sealed with the Drug Inspector's "official lac seal" and 4 sets were made

They sent one set containing15 vaccine vials (unused) and 15 diluents (unused) under cold chain for testing to PHL (Table 10) along with a LRF.

2.4 Dos and Don’ts for collection of vaccine/ diluent samples and transportation

Dos

1. Collect unused samples only from the implicated (suspected) batch.
2. Send the implicated samples of vaccine and diluent to the laboratory affixed with “official lac seal”.
3. Ensure that the accompanying LRF is also affixed with the “official lac seal”.
4. Pack the diluents carefully and separately in a sealed packet.
5. Mention the point from where the vaccines/ diluents were collected on the label of each plastic zipper bag.
6. Ensure the name of the vaccine, batch number, manufacturing and expiry dates and other details on the label as affixed by manufacturer are intact and clearly visible on all the vials/ ampoules of the samples.
7. The packing should be such that there is no breakage of vials. The small cartons in which the vaccines are supplied by the manufacturers may be used for this purpose. The vaccines should be packed in a plastic zipper bag and sealed. The pack is then put in the vaccine carrier or thermocol box with ice packs. (Dry ice may be used for OPV samples and not be used for freeze sensitive vaccines)
8. The address of the PHL and DRA should clearly be written on the box.
9. The samples should be accompanied with the forms and other relevant records if available may be sent.

Don’ts

1. Labels must NEVER be wrapped with adhesive tape or any other labels on the vaccine/ diluent vials as shown in fig 5.3 and 5.4 below
2. There should be no wetting of labels or mutilation. Appropriate labels may be affixed on the zipper bags with vaccine samples inside.
3. The vaccines should not have expired at the time of receipt of vaccine in the laboratory.

Tests done on opened used / partially used vials at Reference Laboratory identified by PHL and WHO

Used (opened) vials are technically not required by the reference laboratory for testing, the sender is however encouraged to send the used vial (if available) to ensure that the same batch of the unused vials are being sent for testing.

The opened vials are **usually not tested** because of following reasons:

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

3. Testing of syringes, needles and samples at reference laboratory identified by PHL and WHO

The identified laboratory where implicated sample of AD Syringes/ Reconstitution Syringes and Vitamin A etc sent by PHL are tested for standard sterility and physical parameters. The testing of the AD syringes/ reconstitution syringes/ and vitamin A should be initiated following decision by the National AEFI committee and DRA and/or when there is clear basis of suspicion and NOT as a routine procedure. Laboratory tests are

performed and results dispatched to the PHL approximately in 60 days of receipt of the samples

3.1 Syringe and needle sample collection

A representative of the DRA (Drug Inspector) and PHL should be involved in the collection and transfer of sealed samples to the reference laboratory. The sample of implicated AD Syringes, Reconstitution Syringes that are sent should be of the same manufacture and batch number. The samples should be collected in 4 equal sets; one set has to be sent for testing; one set retained at the point of collection and two sets retained with the drug inspector (table 5.3). The samples can be sent through reliable courier or postal services. Cold chain is NOT required.

Table 10: Quantity of unused syringes/ needles to be collected for testing

Sample	Unused quantity of implicated batch
AD Syringes	4 Sets of 50 pieces each (total 200) ● 50 pieces to be sent to Reference laboratory ● 50 pieces to be retained at the source of collection ● 2 sets of 50 pieces each (total 100) to be retained by drug inspector (DRA)
Reconstitution Syringes	4 sets of 50 pieces each (total 200) ● 50 pieces to be sent to Reference laboratory ● 50 pieces to be retained at the source of collection ● 2 sets of 50 pieces each (total 100) to be retained by drug inspector (DRA)

3.2 Packing and shipment

- The used samples (AD syringes/ Reconstitution/ Disposable) if available should be sent along with the unused batch of the same manufacturer. Both items should be sealed in separate packets, labeled with the site of collection, placed in a card board box, tied with a string from all sides and an “official lac seal” affixed by the drug inspector.
- The samples should be sent with completed LRF form and forms and other relevant may be sent if requested**.**

Annexure 2:

Guidelines for Initial Management of Anaphylaxis in the Field

Anaphylaxis is one of the most acute life-threatening hypersensitivity reactions that could occur following administration of a vaccine or any pharmacological agent. This could occur very rarely following vaccination, as an allergic reaction to the vaccine or its components.On average when a million is immunized one may develop anaphylaxis. Usually an anaphylactic reaction occurs within minutes of vaccination but in rare instances it could occur even after 12 hours of immunization.

Some people are more prone to develop anaphylaxis. e.g. persons who had developed an allergic reactions to a drug, vaccine or a food previously or those with a history of asthma or eczema. However some people without any such known risk factors could also develop anaphylaxis for the first time.

A person who develops anaphylaxis should be treated immediately to prevent life threatening reactions and death. Hence it is very important to recognize the condition immediately in field clinic settings by the vaccinator, age appropriate first dose of adrenalin 1:1000 to be given immediately and the patient to be taken to the closest hospital for further management as soon as possible.

a) Ensure competency of health care worker administering the vaccine to recognize anaphylaxis early and administer the first dose of adrenaline, by thorough training of all field health staff.

b) Estimate, procure and make available required quantities of Adrenaline 1: 1000 vials and 1 CC disposable syringes with 23 Gauge one inch needles.

Signs and symptoms of Anaphylaxis

Signs and symptoms of anaphylaxis are not distinctive to this condition alone. Signs and symptoms of anaphylaxis could be grouped according to the system of the body that is affected.

1). Skin and mucous membranes.

In over 80 % to 90 % of anaphylaxis reactions, skin and mucous membranes are affected. When only skin and mucous membranes are affected without involvement of other systems it could not be called anaphylaxis. However anaphylaxis could occur without the skin being affected.

- Tingling sensation around the lips

- Oedema of lips
- Itching of skin- specially in small children, scratching of forehead, scratching of hands, scratching of eyes & ears
- Generalized skin erythema
- Urticaria and oedematous patches
- Swelling in the throat (angio-oedema)
- Hoarseness of voice

2). Respiratory system

If a person prone to asthma develops an acute attack of asthma or difficulty in breathing after immunization it should be assumed that this could be a sign of an anaphylaxis reaction instead of assuming it as another attack of asthma and should manage accordingly.

- Cough • Hoarseness
- Wheezing • Rapid breathing
- Difficulty in breathing • Stridor

3). Circulatory system

• Weak peripheral pulse • Increased heart/pulse rate
• Lowered blood pressure • Cold and clammy hands and feet

4). Nervous system

• Feeling of Anxiety and distress • Loss of consciousness

5). Digestive system

• Stomachache (specially in small children) • Vomiting
• Abdominal cramps • Diarrhoea

Diagnosis of anaphylaxis

Following administration of a vaccine to a healthy recipient, if criteria mentioned below are met it could be suspected that the person is suffering from anaphylaxis.

• With rapid onset of occurrence of signs and symptoms
• When two or more of the above systems are affected

Treatment of anaphylaxis

The vaccine recipient with suspected anaphylaxis should never be left alone. Obtain help from those who are around and should ask to arrange transport the patient to the nearest hospital immediately. Vaccine recipient should be stretched out with the airway clear. If the vaccine

recipient is conscious he/she should be kept supine with the feet raised higher than the head. If the patient is unconscious he/she should be kept in the left lateral position.

Adrenaline is the most important and effective drug in the treatment of anaphylaxis. Complications and death could be prevented by giving this drug as soon as possible (with the exception of infants).

Adrenaline 1:1000 solution should be given intra muscular (IM). It should NEVER be given subcutaneous (SC) or intravenous (IV).

It should be given on the middle 1/3 of the anterolateral aspect of the thigh.

In immunization field clinic settings ONLY ONE DOSE of adrenaline should be given. Dosage of adrenaline 1:1000. Anaphylaxis among infants (less than 1 year of age) is very rare and infants should not be given adrenaline in field clinic settings.

Age Dose of Adrenaline (1:1000)

- 12 months to 06 years 0.15 mg (0.1ml)
- 06 years to 12 years 0.2 mg (0.2ml)
- 12 years and over 0.3 mg (0.3ml)

Dose of adrenaline should not be changed even if the child is obese. A one inch 23 Gauge needle could be used to inject adrenaline to make sure it is delivered into the muscle. Before injecting the piston of the syringe should be drawn back to make sure that there is NO blood drawn into the syringe and hence the needle is not in a vein.

Differentiation between anaphylaxis and a fainting attack.

Adults and adolescents could faint due to their fear of the anticipated pain or fear of the injection itself. In the case of infants and preschool children fainting is rare. Hence if an infant or preschool child becomes unconscious after immunization, anaphylaxis should be suspected first.

	Fainting Attack	**Anaphylaxis**
Onset of signs and symptoms	Before immunization Or While immunizing Or Minutes after immunizing	Generally within minutes after immunization Could also occur a few hours after

Skin and mucous membranes	Generalized pallor Cold and clammy hands	· Generalized skin erythema · Itching of the skin (in children specially hands, forehead, eyes and ears) · Tingling sensation around the lips · Urticaria · Swelling of mucous membranes (Angio-oedema)
Respiratory system	Rate of respiration normal Shallow breathing	· Rapid respiratory rate · Difficulty in breathing · Cough · Wheezing · Stridor · Hoarseness of voice · Constrictive feeling of the chest · In drawing of the chest
Circulatory system	· Reduced heart rate · Weak pulse · Transient absence of peripheral pulse · Carotid pulse is strong and easily felt · Blood pressure could dropbut when keeping the patient in supine position blood pressure soon returns to normal	· Increased heart rate · Weak pulse · Pulse not felt sometimes · Carotid pulse weak · Hypotension. · When keeping the patient in supine position blood pressure does not return to normal
Nervous system	· Fiendishness or feeling faintish · Light headedness · Loss of consciousness. · When keeping the patient in a supine position he soon becomes conscious	· Patient is anxious and distressed · Becomes unconscious and keeping the patient in supine position makes no difference
Digestive system	· Vomiting	· Vomiting · Diarrhoea · Stomachache (specially in small children) · Abdominal cramps

Patient details			
Name:		Name of Health Centre	Residential Address
Age	Date of birth	Sex	Hospital reg / MCH card No

Past allergic history: Has the patient had previous allergic reactions? • Yes • No

If 'Yes', Allergen (Drug/Vaccine/Food/Other) - *specify*?

Part I: Clinical features

Date & time of clinical examination: Date(dd/mm/yy)

Time : am/pm

Skin & Mucosa	• Urticaria • Erythema • Pruritus • Prickle sensation				*Specify* the site of reaction:	
	Eye	• Red bilateral • Red unilateral • Itchy				
	Angioedema	• Tongue • Throat • Uvula • Larynx • Lip • Face • Limbs • Other				
Respiratory system	• Sneezing • Rhinorrhoea • Sore throat	• Hoarse voice • Stridor	• Cough	• Tachypnoea • Difficulty in swallowing • Rhonchi	• Wheezing • Indrawing / retractions • Chest tightness	• Grunting • Cyanosis • Difficulty in breathing

Circulatory system	BP (mmHg)	• Decreased central venous pulse	• Capillary refill time >3secs	Heart rate (m)
CNS	• AVPU *		• Other(*specify*):	
GIT	• Diarrhoea	• Nausea	• Abdominal pain/cramp	• Vomiting
Diagnostic Criteria	Brighton Classification Level 1,2,3 **			

Part 2: Suspected Product and exposure Information

Date & Time of drug/vaccine administration: Date(dd/mm/yy)		Time : am/pm	
Drug • Oral • Parenteral	• Vaccine	• Diluent	• Other (*specify*).
Generic name : Name of manufacturer :		Trade name :	
Batch number :	Expiry date :	*For vaccine*: VVM status • I • II • III • IV • 1st dose • 2nd dose • 3rd dose • 4th dose	
If diluent used, specify batch number & expiry date:			
If parenteral medicine/vaccine: • Single dose • Multi dose		• Liquid • Lyophilised	
Route of administration: • Oral • IV • IM • SC • ID • Other(*specify*)			
Site of Administration: • Deltoid • Thigh • Buttock • Other (*specify*)			
Person who administered: • HA • Nurse • Other (*specify*)			
Place of administration/reaction: • Hospital MCH Clinic • BHU • ORC • Other(specify)			

Anaphylaxis Event Record

(To be completed by a Medical Officer)

Annexure 3:

ADVERSE EVENT FOLLOWING IMMUNIZATION REGISTER (To be maintained at all Health Centers)

SL No.	Registration/MCH Card No.	Name & Age	Date of Report/ Detection	Adverse Event	Related Vaccine	Batch No/Lot No.	Date of Immunization	Address and Contact No.	Remarks

Annexure 4 (AEFI FORM 1):
ADVERSE EVENT FOLLOWING IMMUNIZATION CASE NOTIFICATION FORM
(Health Centers to DHO/VPDP)

<table>
<tr><td></td><td colspan="4">Patient Information</td></tr>
<tr><td></td><td colspan="4">Name: Age:
Sex:</td></tr>
<tr><td></td><td colspan="4">Name & Address of the Parent/Guardian :
Mobile No.:</td></tr>
<tr><td></td><td colspan="4">Information on the vaccine</td></tr>
<tr><td colspan="2" rowspan="2">Vaccine</td><td rowspan="2">Route</td><td rowspan="2" colspan="2">Dose
(1st, 2nd , 3rd, 4th)</td></tr>
<tr><td>(Generic name)</td><td>(Trade name)*</td></tr>
<tr><td colspan="2"></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="2"></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="5">Place of vaccination: Hosp. □ BHU □ ORC □ Name of the Health Center</td></tr>
<tr><td colspan="5">Date of vaccination: Time of vaccination:</td></tr>
<tr><td colspan="5">Adverse Events</td></tr>
<tr><td colspan="2">Local Adverse Events Requiring investigation</td><td colspan="3">Injection site abscess □ BCG Lymphadenitis □ Severe local reaction □</td></tr>
<tr><td colspan="2">CNS Adverse Events Requiring investigation</td><td colspan="3">Vaccine associated paralytic poliomyelitis □ GBS □ Encephalopathy □ Encephalitis
□ Meningitis □ Seizures Febrile □ Seizures Afebrile</td></tr>
<tr><td colspan="2">Other Adverse Events</td><td colspan="3">Anaphylaxis □ Persistent screaming □ Osteitis / Osteomyelitis □ Hypotonic Hyporesponsive Episode □</td></tr>
</table>

Requiring investigation	Toxic Shock Syndrome □
Adverse Events Not Requiring investigation	Allergic reaction □ Arthralgia □ High fever (>39°C / 102°F) □ Nodule at the injection site □
Other Adverse Events	
Date & Time onset of adverse event:	
Date & Time referral to higher centre:	

Medical History/other	**Outcome:**
	Hospitalized: Yes No if 'Yes', Hospital Registration No: Still in the hospital/BHU □ Discharged □
	Recovered completely □ Recovered partially □ Death □

Reporting source: Date of the notification Name of the Health Center:

Name & Signature of the notifying officer: Mobile No.

Annexure 5 (AEFI FORM 2):

ADVERSE EVENT FOLLOWING IMMUNIZATION MONTHLY SUREVILALNCE REPORTING FORM (DHO to VPDP)

Name of district: …….. Month: ……. Reporting date: ……

Adverse Event	BCG	OPV	Penta	MR	DPT	Td	IPV	HPV	HepB	Others
Local adverse events requiring investigation										
1) Injection site abscess										
2) BCG lymphadenitis										
3) Severe local reactions										
CNS adverse events requiring investigation										
Vaccine associated paralytic poliomyelitis										
Gullian Barre syndrome										
Encephalopathy										
Encephalitis										
Seizures										
Other adverse event requiring investigations										
Death										
Anaphylactic shock										
Persistent screaming										
Hypotonic Hyporesponsive Episode (HHE)										
Toxic shock syndrome										
Osteitis /Osteomyelitis										
Adverse events not requiring investigations										
High fever										
Allergic reaction										
Arthralgia										
Others										

Additional Comments

……
……

Annexure 6 (AEFI FORM 3):

ADVERSE EVENT FOLLOWING IMMUNIZATION CASE INVESTIGATION FORM

A. PATIENT INFORMATION

A.1. Name of the patient A.2. Hospital registration No.:

A.3. Residential address:

A.4. Date of birth: A.5. Gender: Male/Female

A.6. Interview details (from whom, where and when):

B. PRESENT ILLNESS / OUTCOME:

B1. What is the reported AEFI? …….. B2. Date of onset □□ / □□ / □□ dd / mm yy B3. Where was the patient treated? □ 1. Hospital □ 2. BHUs	B4. Was patient admitted to hospital Yes □ . No. □ Unknown □ B5. If yes, date of admission: □□/□□/□□ dd /mm/yy B6. Name of hospital/BHU…….	B7. Outcome Recovered □ Died □ Unknown □ B8.Date of discharge, Refer or death Date: □□/□□/□□ dd /mm/yy B9. If referred, name of the hospital …….

C. CLINICAL DATA

C1. Symptoms and signs	C2. Date of onset dd /mm/yy	C3. Laboratory investigation (Attach copy of the results)
□ Fever □ Inconsolable crying □ Painful swelling at the injection site □ Enlarged tender axillary lymph nodes □ Convulsions □ Altered sensorium □Cough/ fast breathing □Grunting/cyanosis □Chest retraction □Cold peripheries □Pale skin Any other symptoms and signs ……	□□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□ □□/□□/□□	□Hematological (CBC, Diiff) □Biochemistry (LFT, RFT, Electrolytes, lactate, CPK, ABG) □Microbiology (biological material-microscopic examination, gram stain, culture) □Serology (viral markers, antibody) □Radiology (Cxray, USG, CT) □ Cerebrospinal fluid analysis □Histopathology □Other tests

C.4. Drugs given and their routes of administration	C.5. Treatment & management
1. 2. 3. 4. 5.	
C6. Diagnosis	

D. PAST MEDICAL AND FAMILY HISTORY

		Yes	No	Unknown	if yes (specify) No and Place
D1.	Existing congenital disease	☐	☐	☐	……
D2.	Persisting underlying disease	☐	☐	☐	……
D3.	Previous history of significant illness	☐	☐	☐	……
D4.	Previous history of hospitalization	☐	☐	☐	……
D5.	Family history of similar even	☐	☐	☐	……
D6.	Previous history of similar event	☐	☐	☐	……
D7.	Past medication use (including alternative medicines)	☐	☐	☐	……

E. OTHER RELEVANT HISTORY

E1 When was the child last well? Date: …….

E2 Occupation of the parents ……

E3 Daytime child care giver ……

		Yes	No	Specify
E4	Delays in taking patient to the hospital	☐	☐	……
E5	Delays in transferring patient to the referral hospital	☐	☐	……
E6	Delays in receiving treatment	☐	☐	……
E7.	Alternative practices available in the area and their utilization by the index family	☐	☐	……

F. IMMUNIZATION HISTORY

F1. Date of immunization: F2.Time of immunization:

F3. Place of immunization: F4. Hospital/BHU/ORC

F5. Type of vaccine (please √ appropriate box)	F6. Name & Dose	F7. Expiry Date	F8. Batch No.	F9. Mfd. by
□BCG □OPV □Penta □MR □DPT □Td □HepB □IPV □HPV □Others (specify)				
F10. Diluents				

G. INFORMATION ON COLD CHAIN /STORAGE / VACCINATION TECHNIQUE

G1. Refrigerator	G2. Vaccine status	G3. Vaccine stock	G4. Cold chain status
G1.1 Vaccines are stored in correct order? YES □ NO□ G1.2 Anything other than vaccine stored? YES □ NO□ G1.3 Refrigerator inventory YES □ NO□ G1.4 Date of receipt…… G1.5 Functional YES □ NO□ G1.6 First In and First Out (FIFO) and First Expiry First Out (FEFO) YES □ NO□	G2.1 Vaccine transported in a □Vaccine carrier □Cold box □Others (specify) …… G2.2 Date of open vial ……. G2.3 Physical appearance of the vaccine ……..…	G3.1 Stock balance of Vaccine …….. Diluent …… G3.2 Difference if any, between quantity received and used Vaccine …… Diluent …….	G4.1. VVM stage……□ G4.2. Temperature in the main compartment of the refrigerator ……. G4.3 Status of the log tag for 1 month period prior to the date of the immunization: Maximum…… Minimum……

At the time of the observation of the immunization	Satisfactory	Unsatisfactory	Not observed
G5. Maintenance of cold chain 1. Packing of vaccine	□	□	□

2. Maintenance of cold chain in unopened/opened vials during immunization	□	□	□
G6. Prevaccination screening	□	□	□
G7. Vaccination procedure	□	□	□
1. Reconstitution	□	□	□
2. Drawing of vaccine			
3. Injection technique			
G8. Please √ the appropriate box Reusable □ Disposable □ AD syringes □			

H. Service provision capacity

H1. Human resource capacity	H2. Guidelines	H3. Service M & E
H1.1 Number of staffs trained in immunization practices…… H1.2 Children load per immunization session…… ….. H1.3 Training on immunization How often ……. H1.5 Date of last training ……	H2.1 Guideline related to EPI …… …….	H3.1 Is there any system of monitoring & evaluation of staff performance on immunization? YES □ NO□ H3.2 Date of last supervisory visit for immunization practice …….. (attach feedback report)

I. Epidemiological data on the AEFI

Any history of similar events reported among those vaccinated	No	Yes	Unknown
H1. At the same clinic session	□	□	□
H2. Using same vaccine at previous session at the same health center	□	□	□
H3. Using same vaccine at the other health center	□	□	□
H4. History of similar events reported among those unimmunized	□	□	□
H5. Among the same age group children (vaccinated/unvaccinated)	□	□	□

J. **Regulatory provisions assessment**

Topic	**Response**
Antigen Type	Recombinant Attenuated Live Killed
Status of Registration	WHO Prequalified Not WHO pre-qualified
Certificate of Lot Release from NRA of Exporting Country	Yes No
Certificate of Lot Release from DRA	Yes No
Lot/Batch Tracking Record from Manufacturer	Yes (Other countries supplied to and doses) No
Lot/Batch Tracking Record within country	Yes (Other countries supplied to and doses) No
Vaccine Product Information Sheet Available	Yes No
Vaccine Safety Information Sheet from WHO Available	Yes No
Vaccine Safety Information Sheet from Manufacturer Available	Yes No

K. Assessment of VPDP & laboratory capacity

Topic	**Response**
Lot/Batch Tracking Record within country	Yes No
Distribution of cases	Single Single-site Cluster Multi-site Clusters

Training of Vaccinator	% of vaccinators trained in last 3 years in EPI practice _____
EVM Assessment conducted in last 3 years	□Yes (include the latest status report of indicators) □No (conduct rapid assessment of CCL at central level)
National Laboratory has capacity to test vaccine and tissue samples	□Yes □No

I. **CONCLUSION AS TO THE CAUSE OF AEFI**

Immunization errors related reaction Event caused by an error in vaccine preparation handling or administration	Vaccine product related reaction Event caused by the inherent properties of the vaccine	Vaccine quality defect of the related reaction Event caused due to quality defects of the vaccine product	Immunization anxiety related reaction Event from anxiety about or pain from the injection itself rather than the vaccine	Coincidental events Event that happens after immunization but not caused by the vaccine- a chance association	Unknown
If possible, describe the cause in below given area					

Corrective action taken
…….....

Remarks
…….....

Signature …… Name

…….. Date …….

Designation …….

Annexure 7 (AEFI FORM 4):

DEATH INVESTIAGTION FOLLOWING IMMUNIZATION FORM
(Hospitals to VPDP)

Name of child: **Date of death:**

Name of investigator: **Contact no:**

Hospital Registration No:

1). Investigation of sequelae leading to death and past history

Identification and related basic information	
Name, address and contact number of the parent	
Date of birth	
Age on the date of immunization	
Sex	
Birth weight	
Weight on the date of immunization	
Responsible vaccine (if known)	
Date and time of vaccination	
Time interval between immunization and death	

2). Clinical description of the event as described by the mother

2.1 Assessment of the child before the immunization

- Feeding…….
- Activity……..
- Features of any acute illness prior to immunization (specify)
  ……
  ……
  ……
  …
- Any medication in last 24 hours prior to immunization. Yes or No. If yes , please specify

Drug	Dose	Time of last dose

3). Assessment of the child during immunization

- Incriminated Vaccine ……. Date and time of vaccination

- Medications given with vaccination

……

- Description of significant adverse event noted by mother

……..……
……
……
……

3.1. Measures taken by mother / guardian to overcome the adverse event

1. Treatment at another health centre
   ……..
2. When was the child taken to the hospital……
3. Diagnosis made at this health centre……
4. Medicines prescribed, dose frequency and time of last dose
   ……
   ……
   ……
5. Traditional medicine, specify (if applicable)
   ……
   ……
6. Any other measures/treatments
   ……
   ……
   ……
   ……
7. Outcome of the above measures on the observed adverse event
   ……
   ……
   ……
   ……

3.2. Was the child hospitalized? YES/NO

If yes, give details as per mother/attendant……

3.3 Description of final event as per mother

……..……
……
……
……

3.4 Was the child sleeping at the time of death? If yes, give details. Sleeping place, sleeping position, other people sleeping in the same place

……
……..
……
……

4). Antenatal and birth history

- Antenatal complications:
- Place of birth:
- Mode of deliver:
- APGAR score:
- Significant finding in neonatal examination:

5) Developmental history

……
……
……
……

6). Past medical history

……
……
……

7). Congenital or acquired disease for which the child is on treatment

……
……----------

8). Previous immunization

Vaccine	Date	Batch	Adverse event

9). Family and social history

- Smoking and alcohol use:
- Neonatal or infant death in family:
- Details of siblings:
- Medical history of siblings:

10). Details of management of the case at the hospital

- Name of the hospital:
- Date and time of admission:

- Name of doctor taking care of the patient:

Clinical description and clinical findings as per admitting doctor

……
……
……
……
……

Details of subsequent management as per records

……
……
……
……

Investigations

	Investigation	**Interpretation**
Hematological		
Biochemistry		
Radiological		
Others		

Management

- **Pharmacological:**
- **Non-pharmacological:**
- **Probable diagnosis:**