# National Guideline on Surveillance of Adverse Events Following Immunization (AEFI)

## Royal Government of Bhutan Ministry of Health

3rd Edition 2025

Vaccine Preventable Diseases Program
Department of Public Health
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# FOREWORD

Vaccination is one of the most effective public health interventions, saving millions of lives and preventing the spread of infectious diseases worldwide. While vaccines undergo rigorous testing and monitoring to ensure their safety and efficacy, no medical intervention is entirely risk-free. Adverse Events Following Immunization (AEFI), both minor and, in rare cases, serious, can occur. However, serious vaccine-related adverse events remain exceptionally rare.

Since 2003, Bhutan has implemented a robust AEFI surveillance system to monitor vaccine safety and maintain public confidence in immunization. This system is essential for distinguishing true AEFI cases from unrelated events, promptly addressing potential issues, and ensuring the continued safety of vaccines. AEFI surveillance enhances immunization program quality, reinforces public trust, and strengthens the capacity to respond to unforeseen events.

All AEFIs, regardless of severity, should be reported, while serious cases must be thoroughly investigated and addressed with appropriate corrective measures. Doing so safeguards public health, strengthens confidence in the immunization program, and ensures the continued success of vaccination efforts. By closely monitoring AEFI data, we can identify trends, take preventive actions, and further improve immunization practices. This guideline is intended to provide health workers at all levels with the knowledge, resources, and procedures required to effectively monitor, report, and investigate AEFIs. By following these guidelines, we aim to strengthen our AEFI surveillance system, safeguard public health, and maintain the trust and confidence of the Bhutanese community in our national immunization efforts.

Tashi Delek!

Karma Jamtsho
**Director**
**Department of Public Health**

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# CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AEFI | Adverse Events Following Immunization |
| AFP | Acute Flaccid Paralysis |
| BCG | Bacillus Calmette-Guerin |
| BFDA | Bhutan Food and Drug Authority |
| BHU | Basic Health Unit |
| CSF | Cerebrospinal fluid |
| CMO | Chief Medical Officer |
| DHO | Dzongkhag Health Officer |
| DTP | Diphtheria Tetanus Pertussis |
| DT | Diphtheria Tetanus |
| EPI | Expanded Program on Immunization |
| HA | Health Assistant |
| Hep. B | Hepatitis B |
| Hep. C | Hepatitis C |
| HHE | Hypotonic Hyporesponsive Episodes |
| IPV | Inactivated Polio Vaccine |
| MoH | Ministry of Health |
| MS | Medical Superintendent |
| MO | Medical Officer |
| NITAG | National Immunization Technical Advisory Group |
| OPV | Oral Polio Vaccine |
| ORC | Out Reach Clinic |
| RRH | Regional Referral Hospital |
| TSS | Toxic Shock Syndrome |
| VVM | Vaccine Vial Monitor |
| VPDP | Vaccine Preventable Disease Program |
| WHO | World Health Organization |

# CHAPTER 1: INTRODUCTION

Immunization is an effective preventive health intervention, significantly reducing the burden of vaccine-preventable diseases (VPDs) and protecting public health. Modern vaccines are safe, with ongoing advancements improving their safety, quality, and efficacy. However, no vaccine is entirely risk-free. As new vaccines, including those for emerging diseases, are introduced, the likelihood of detecting AEFIs may rise with increased usage. Nonetheless, the benefits of vaccination far outweigh any actual or perceived risks. AEFI range from mild side effects to rare life-threatening cases, with most serious events being coincidental or resulting from errors in administration or handling errors. Regardless of the specific cause, an AEFI can raise public suspicion, leading to vaccine hesitancy and increased risk of severe vaccine-preventable diseases.

AEFI surveillance is essential for ensuring immunization safety and acceptance. Like other disease surveillance systems, it systematically collects data on post-vaccination events to support effective management, restore public confidence, and prevent inappropriate responses. The whole cycle of surveillance depends on the process of AEFI detection and reporting by health professionals untill the dissemination of feedback by the program.

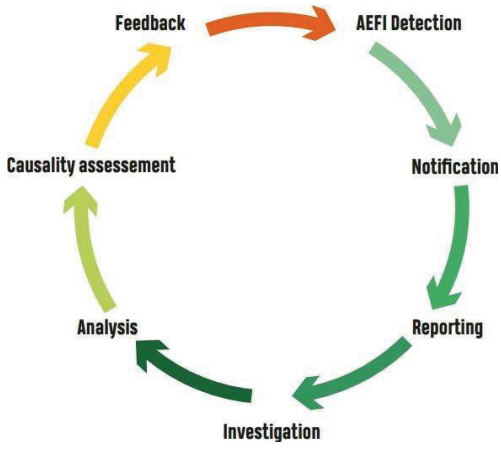



*Figure 1.1: The cyclic flow of the AEFI surveillance*

Bhutan boasts a robust and well-established immunization program under the Ministry of Health (MoH). The country offers free immunization services through the Expanded Program on Immunization (EPI), which was launched in 1979 to reduce vaccine-preventable diseases. The program encompasses all districts (Dzongkhags) and ensures that vaccines reach even remote areas through outreach services. Key aspects of immunization include universal coverage to achieve high immunization rates and ensuring all children receive vaccines. Routine immunization is administered through Primary Health Centres, regional and district hospitals, and outreach clinics. The National Immunization Schedule includes vaccines against tuberculosis, diphtheria, pertussis, tetanus, hepatitis B, Haemophilus influenzae type B, polio, measles, rubella, mumps, pneumonia, HPV and influenza. During the COVID-19 pandemic, Bhutan introduced COVID-19 vaccines and achieved high coverage rates. Cold chain management ensures vaccine potency by maintaining the required temperature conditions. School-based immunization provides HPV and other booster doses through school health programs.

Bhutan has a robust AEFI surveillance and reporting system to ensure vaccine safety and maintain public confidence. The system was initiated in 2003, and in 2015, the first AEFI guideline was developed to establish the AEFI surveillance network and enhance nationwide awareness among health facilities, hospitals, and field workers.

The guideline emphasizes immediate reporting of serious adverse events to health centres and the MoH within 24 hours. It also describes types of AEFI classifications, such as vaccine-related, vaccine quality-defect related, programmatic error, coincidental, and unknown causes. Additionally, it outlines the role of the Bhutan Food and Drug Authority (BFDA) in overseeing vaccine safety with technical guidance from the National Immunization Technical Advisory Group (NITAG). District and national AEFI committees are responsible for investigating serious cases and making necessary policy adjustments. Community awareness of AEFI reporting should be strengthened through public education by health workers at community

meetings and via digital platforms. However, over time challenges related to AEFI monitoring and proper documentation have been noted. To address these challenges and to update the roles and responsibilities of key stakeholders, the revised guidelines have been developed.

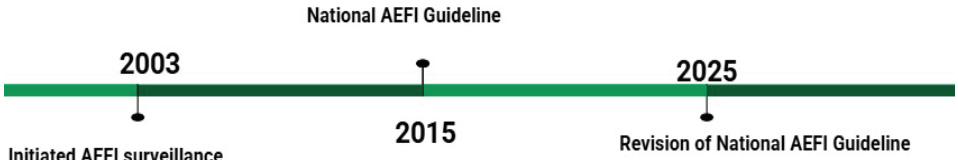



*Figure 1.2: Milestones in AEFI program implementation in Bhutan*

To foster public confidence in immunization, both the public and healthcare professionals must be well-informed and equipped to address vaccine safety concerns. Timely responses and clear communication are essential to maintain trust and program integrity. As public awareness of vaccine safety increases, so does the demand for transparency. Effective responses require a detailed investigation followed by causality assessment to distinguish between true vaccine-related events and coincidental events, supported by scientific analysis and expert input. Health workers must be prepared to initiate prompt and decisive responses to any AEFI, thereby preserving lives, preventing recurrence, and upholding public trust.

## 1.1 Scope

This guideline is intended for health professionals, program managers, AEFI committee members, drug regulators, medical universities, and other stakeholders involved in vaccine safety and quality at various levels. It outlines strategies to ensure vaccine safety by : AEFI surveillance, reporting, investigation, causality assessment, and clear communication to address immunization safety concerns.

## 1.2 Objective

The objective of this guideline is to provide technical and operational updates on the improvements made to the AEFI surveillance system. It aims to enhance the efficiency and effectiveness of immunization programs at all

levels, thereby ensuring the safety of all vaccine recipients and sustaining high vaccination coverage.

### 1.2.1 Specific Objectives

- Early detection and timely response to AEFIs
- Timely submission of the report using the standardized reporting form
- Timely implementation of corrective and preventive measures for AEFI
- Improved documentation of both serious and minor AEFI
- Conduct causality assessment of all serious AEFI and disseminate findings
- Enhance awareness among : parents, guardians, communities, media, and stakeholders, on AEFIs through effective communication

# CHAPTER 2: ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

The national immunization program uses vaccines that are extremely safe and effective. However, no vaccine is 100% safe.Furthermore, the immunization procedure itself is a potential source of AEFIs. AEFI is defined as “any untoward medical occurrence following immunization which does not necessarily have a causal relationship with the usage of the vaccine”. An AEFI can also include any unfavourable or unintended symptoms, clinical signs, abnormal laboratory finding, or disease.

Reported AEFI can be either true adverse events caused by the vaccine or the immunization procedure, or coincidental events that are unrelated to immunization and are only temporally associated with it.

*Table 2.1: Types of AEFI and definition*

| 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

Based on the specific cause, seriousness and frequency of AEFI, vaccine reactions may be grouped into two broad categories as follows:

### 2.1.1 Specific vaccine reactions

- Vaccine product-related reaction;
- Vaccine quality defect-related reaction;

### 2.1.2 Vaccine reactions by seriousness and frequency

- Minor reactions (which are usually common)
- Serious reactions (which are usually rare)

**Vaccine reactions by seriousness and frequency**

Some AEFI occur more frequently than others. Minor AEFI are more common compared to serious AEFI. Understanding the frequency of various AEFI is crucial for identifying clusters of events within a specific time period.

Table 2.2 presents the frequency rate, in percentage, for each AEFI category.

*Table 2.2: Frequency rate for AEFI category*

| Frequency category | Frequency in rate | Frequency in % |
|---|---|---|
| Very common | ≥ 1/10 | ≥ 10% |
| Common | ≥ 1/100 to < 1/10 | ≥ 1% and < 10% |
| Uncommon | ≥ 1/1,000 to < 1/100 | ≥ 0.1 % and < 1% |
| Rare | ≥ 1/10,000 to < 1/1,000 | ≥ 0.01% and < 0.1% |
| Very rare | < 1/10,000 | < 0.01% |

### 2.2.1 Minor vaccine reactions

*Table 2.3: Frequency and nature of minor AEFI against specific antigens*

| Vaccine[a] | Frequency (%) | | |
|---|---|---|---|
| | Local reactions | Systematic reactions | |
| | Pain, Swelling, Redness | Fever >38°C | Irritability, malaise and non-specific symptoms |
| BCG | 90% to 95% | - | - |
| Hepatitis B | Adults up to 30% | 1 to 6% | - |
| Hib | Children up to 5% | 2 to 10% | - |
| Measles/MMR | 5 to 15% | 5 to 15% | Up to 5% (rash) |
| OPV | Up to 10% | Less than 1% | Less than 1%b |
| Tetanus/DT/Td | None | Up to 10% | Up to 25% |
| Pertussis (DPT-Whole cell)[d] | Up to 10%c | Up to 50% | Up to 60% |
| IPV | Up to 50% | - | - |
| PCV | ~ 30% | ~ 20% | ~ 20% |

### 2.2.2 Rare and serious vaccine reactions

Serious vaccine reactions such as seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE), and 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 program error. The frequency and nature of rare, serious vaccine reactions are outlined in Table 2.4.

Most vaccine reactions are minor, self-limiting, and occur as the immune system responds to the vaccine. These minor reactions may include local

site reactions (e.g., pain, redness, swelling) and general systemic symptoms such as fever, vomiting, loss of appetite, diarrhoea, and malaise. For example, these local reactions are reported very commonly (>10%) with whole-cell DTP antigen, whereas for acellular DTP antigen it is only a common reaction with a frequency of 1-10%.In some of the cases of the non-antigenic vaccine components (e.g., adjuvants, stabilizers, or preservatives) may also cause these vaccine reactions. The frequency and nature of common, non- serious vaccine reactions are outlined in Table 2.3. If the observed rate of reactions rate

*Table 2.4: Frequency and nature of serious AEFI against specific antigens*

| Vaccine | Reactions | Time-to-Onset of Event | Frequency per Doses given |
|---|---|---|---|
| BCG Hib | Suppurative adenitis<br>BCG Osteitis | 2 to 6 months<br>Up to several years | 100 to 1000 |
| | Disseminated BCG infection None known | 1 to 12 months;<br>- | - |
| Hep B | Anaphylaxis Febrile seizures | 0 to 1 hour<br>5 to 12 days | 1 to 2<br>330 |
| Measles/ MMR[a] | Thrombocytopenia (low platelets) Anaphylaxis | 60 days<br>0 to 1 hour | 30<br>1 |
| OPV | Vaccine-Associated Paralytic Poliomyelitis<br>Brachial Neuritis | 4 to 30 days<br>2 to 28 days | Up to 0.4[b]<br>5 to 10 |
| Tetanus | Anaphylaxis | 0 to1 hour | 1 to 6 |
| | Sterile abscess | 1 to 6 weeks | 6 to 10 |

| Vaccine | Reactions | Time-to-Onset of Event | Frequency per Doses given |
|---|---|---|---|
| DPT | Persistent (>3 hours) inconsolable screaming<br>Seizures | 0 to 48 hours<br>0 to 3 days | 1,000 to 60,000<br>600[c] |
| | Hypotonic Hypo Responsive Episode (HHE)<br>Anaphylaxis/Shock | 0 to 24 hours<br>0 to 1 hour | 30 to 990<br>1 to 6 |
| HPV | Anaphylaxis, Myalgia, Arthralgia | 0 to 1 hour | 1-28 per 100 doses<br>1.7 per 1,000,000 doses |
| Influenza (Inactivated) 22 | Anaphylaxis<br>Guillain-Barré syndrome<br>Oculo-Respiratory Syndrome | 0 to 1 hour<br>2 to 7 weeks<br>2 to 24 hours | 0.7 per 1,000,000 doses<br>1–2 per 1,000,000 doses<br>76 per 1,000,000 doses |

a *Most 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 the 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*

## 2.3 Prevention of vaccine reactions

Vaccines are rarely contraindicated, but screening for contraindications is essential to prevent serious reactions. For example, vaccines are contraindicated if there is:

- Serious allergy (anaphylaxis) to the vaccine or its excipients.

- Progressive neurological illness
- Immunodeficiency (in the case of live vaccines)
- Pregnancy (for certain vaccines)

## 2.4 Immunization error-related reactions

The term "Immunization error-related reactions" refers to errors resulting from all errors that occur after a vaccine product has left the manufacturing or packaging site. These stages include: prescribing, preparation, handling, storage and administration of the vaccine. This type of AEFI was earlier categorized as "program error." However, the terminology has been later updated to Immunization error-related reactions to emphasize the errors related with vaccine delivery process. Immunization error related reactions are preventable, and can significantly undermine the trust in immunization programs (Table 2.5). Timely identification and correction of these errors are therefore crucial for maintaining the safety and credibility of immunization efforts.

*Table 2.5: Common program errors leading to AEFI*

| Immunization error | | Related reaction |
|---|---|---|
| Error in vaccine handling | Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents, where applicable) | Systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines |
| | Use of a product after the expiry date | Failure to protect as a result of loss of potency or no viability of an attenuated product |

| Immunization error | | Related reaction |
|---|---|---|
| Error in vaccine prescribing or non-adherence to recommendations for use | Failure to adhere to a contraindication | Anaphylaxis disseminated infection with a LAV, e.g., Disseminated BCG |
| | Failure to adhere to vaccine indications or prescriptions (dose or schedule) | Systemic and/or local reactions, neurological, muscular, vascular or bony injury due to incorrect injection site, equipment or technique |
| Error in administration | Use of an incorrect diluent or injection of a product other than the intended vaccine | Failure to vaccinate due to incorrect diluent, reaction due to inherent properties of whatever was administered other than the intended vaccine or diluent |
| | Incorrect sterile technique or inappropriate procedure with a multidose vial | Infection at/beyond the site of injection |

### 2.4.1 Prevention of Immunization errors (Program errors)

- It is both important and necessary to maintain the cold chain at all levels
- Vaccines must only be reconstituted with the diluent supplied by the manufacturer
- Reconstituted vaccines should be used within six hours after reconstitution; it must be discarded at the end of each immunization session and should never be retained
- No other drugs or substances should be stored in the same refrigerator where the vaccines are stored
- Immunization staff must be adequately trained and closely supervised to ensure that proper procedures are being followed

- Careful epidemiological investigation of an AEFI is needed to understand the cause and to correct immunization practices
- Prior to immunization, adequate attention must be given to contraindications

## 2.5 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 the 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 program. If the same event is also observed among the same age group and around the same time who did not receive the suspected 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 help to determine possible 'signals' and to correctly categorize them as coincidental events.

## 2.6 Immunization anxiety-related reactions

An individual or a group can become stressed and may react in anticipation to immunization as a result may cause immunization-related anxiety reactions. This reaction is unrelated to the content of the vaccine. Commonly reported immunization anxiety-related reactions are:

- Fainting
- Hyperventilation
- Vomiting

These can be reduced by minimizing stress in those awaiting injection through short waiting times, comfortable room temperatures, and preparation of vaccine out of recipient view and privacy during the procedure. In a group situation, mass hysteria is possible, especially if a recipient has fainted or has had some other reaction following vaccination. A fainting episode can be misdiagnosed as anaphylaxis. Health workers need to be able to differentiate between the two conditions. In such situations, health workers should provide proper counselling and reassure the recipient and accompany parents/guardians.

## 2.7 Serious Events

Serious AEFIs are defined as those that are life-threatening and those that result in hospitalization, 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 clusters, serious events of unexplained aetiology occurring within 30 days after a vaccination, and events causing significant parental or community concern.

## 2.8 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, the same batch number and 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 the same vaccinator or the same batch of the vaccine will be considered clusters.

## 2.9 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 and 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.

# CHAPTER 3: AEFI SURVEILLANCE SYSTEM

AEFI surveillance is a critical component of immunization safety, ensuring the timely detection, reporting, investigation, and management of AEFI. It involves systematic monitoring of vaccine quality, storage and handling, administration practices, and, where relevant, waste management practices that may impact injection safety. A well-functioning AEFI surveillance system enables early identification of potential safety signals, facilitates causality assessment, and supports evidence-based responses to maintain public confidence in immunization programs.

Figure 3.1 illustrates an overview of the AEFI surveillance system in Bhutan.

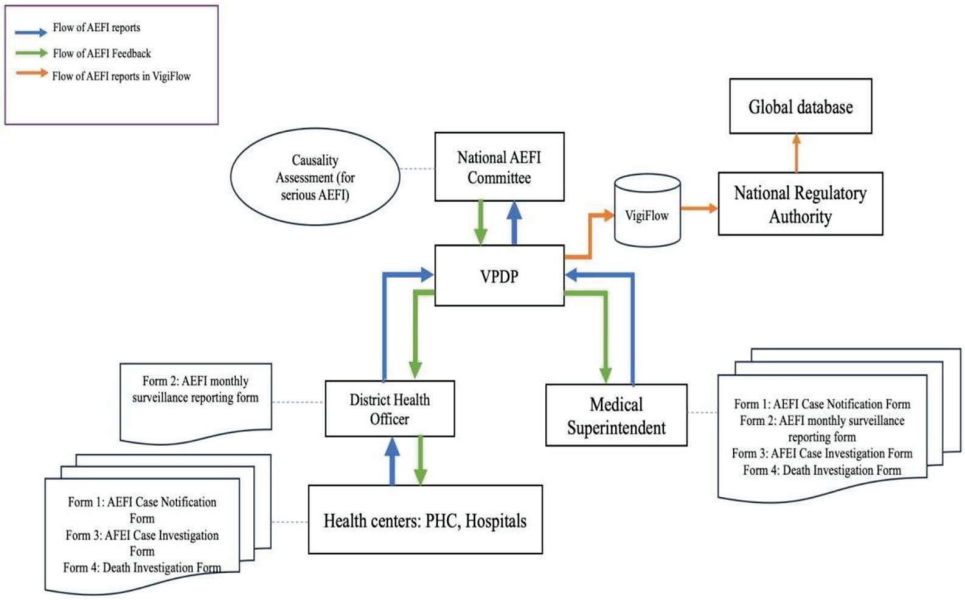



*Figure 3.1: An overview of the AFEI surveillance system in Bhutan*

- All AEFI should be reported by the health centre using the AEFI reporting form (Annexure I) to MS/CMO.
- Serious AEFI needs to be reported immediately.
- The MS/CMO should then verify the AEFI reporting form, determine the requirement of investigation and then submit the completed AEFI reporting form to VPDP.

- In terms of serious AEFI requiring investigation, the district AEFI Committee led by the CMO/MS in coordination with the DPHO/TPHO should investigate using the AEFI investigation form (Annexure II).
- Any deaths with a temporal association with vaccination must be investigated by the district AEFI Committee using the "Investigation of Death Following Immunization" form (Annexure III) by the district AEFI Committee.
- The AEFI reporting form and investigation reports must be submitted to VPDP.
- Then the program will submit all the reports to the national AEFI committee for causality assessment.
- The findings from the causality assessment should be submitted to the VPDP. The program will submit the findings for appraisal to the NITAG and communicate with the BFDA and other relevant stakeholders to strengthen the surveillance system.

AEFI surveillance can be classified as active and passive surveillance system

### 3.1 Active surveillance

Active surveillance is primarily used for characterization of the AEFI profile, rates and risk factors. However, its application is limited due to logistical and resource constraints. It involves epidemiological studies (e.g., cohort studies, case-control studies, and case series) to enhance immunization safety surveillance. These studies focus on specific vaccine safety concerns, such as evaluating causality hypotheses.

### 3.2 Passive surveillance

Passive surveillance involves the spontaneous reporting of AEFIs by health care providers, patients or care givers to the first administrative level (DHO/MS/CMO) in the surveillance system. As anyone can report AEFI, passive surveillance offers broad coverage and can help indicate unexpected AEFI. Therefore, the main strength of passive surveillance is to detect early unknown serious AEFI (referred to as "signals").

## 3.3 Case definitions used in surveillance AEFI

*Table 3.1: List of AEFI Case definitions used in surveillance*

1. **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.

***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*

2. **Lymphadenitis (includes suppurative lymphadenitis):** occurrence of either:

- At least one lymph node, 1.5 cm 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)

3. **Severe local reaction:** Redness and/or swelling centred at the site of injection and one or more of the following:

- Swelling beyond the nearest joint
- Pain, redness and swelling of more than 3 days duration or
- Requires hospitalization

Local reactions of lesser intensity may occur commonly and are generally of little consequence. For monitoring purposes, priority should be given to severe local reactions as defined above.

4. **Vaccine-Derived Paralytic Poliomyelitis:** Acute onset of flaccid paralysis within 4– 30 days of receipt of the oral poliovirus vaccine (OPV) or within 4–75 days after contact with a vaccine recipient, with neurological deficits remaining 60 days after onset or death.

5. **Guillain-Barré 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 within 30 days after immunization should be reported.

6. **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 alteration in level of consciousness lasting for one day or more; and
- Distinct change in behaviour lasting one day or more.

Cases occurring within 72 hours after vaccination should be reported.

7. **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.

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

9. **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.

10. **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.

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

12. **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.

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

| |
|---|
| 14. **Toxic- shock syndrome:** Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization, often leading to death within 24-48 hours. |
| 15. **Allergic reaction:** Characterized by one or more of the following (1) skin manifestations (e.g., hives, eczema); (2) wheezing; (3) facial or generalized oedema. |
| 16. **Arthralgia:** Joint pain usually including the small peripheral joints.<br>• Persistent: Joint pain lasting longer than 10 days<br>• Transient: Joint pain lasting up to approximately 10 days |
| 17. **High fever (>39 0 C / 1020F):** The Endogenous elevation of at least one measured body temperature >39 C /102 F |
| 18. **Fever with rash** occurring within 7–60 days after MMR vaccination should be reported. |

## 3.4 Role and responsibilities of key players

The AEFI surveillance system involves a network of key health professionals. The following section outlines the roles and responsibilities of each health professional at various levels of health facilities where immunization service is provided.

### 3.4.1 Health professional providing vaccination

- Screen for previous AEFI before administering the vaccine .
- Provide health education on AEFI identification and home management after vaccination.
- Ensure a 30-minute observation period for immediate AEFI after any vaccination.
- Provide immediate treatment for AEFI and refer to higher centres if required.

- Report any AEFI in reporting Form 1 (Annexure I) and communicate to the CMO/MO/MOIC/ MS. Keep a copy of the report filed at the health centre.
- Submit a monthly zero report to the DHO/MS.
- Maintain the monthly AEFI surveillance report form.
- Ensure that functional emergency kits are available at all times.
- Communicate and share the results of investigations with other health workers and the community, as required.
- Provide awareness and educate the community regarding AEFIs.

### 3.4.2 Chief Medical Officer/Medical Officer In-charge

- Ensure all notified AEFIs are diagnosed according to the defined case criteria, thoroughly verified.
- Mandate health professionals to report AEFIs and submit monthly zero reports when no AEFI is observed.
- Manage AEFI cases effectively and refer to higher centers if necessary for further investigation or treatment.
- Coordinate the collection of appropriate samples and their referral for testing, along with the required completed documentation (as outlined in Annexure I).
- Provide continuous guidance and adequate training to field health workers on AEFI identification, management, and reporting.
- Assist the National AEFI Committee in conducting AEFI investigations when needed.
- Support and facilitate laboratory assessments when required to ensure accurate diagnosis and safety monitoring.
- Ensure the availability of all necessary emergency drugs and medical supplies to effectively and immediately manage AEFIs.
- Maintain well-equipped and functional emergency kits and ensure they are available at all times for immediate use.

- Conduct monthly or quarterly integrated VPD surveillance to ensure ongoing monitoring and reporting.
- Sensitize and educate the community about AEFIs to improve awareness and timely reporting.

### 3.4.3 Medical Superintendent/Chief Medical Officer

- Establish a functional district AEFI committee with a clearly defined ToR.
- Ensure complete documentation of AEFI surveillance at all levels of health facilities.
- Ensure availability of adequate AEFI reporting form, case investigation form, and death investigation form in all the health centres as required.
- Ensure that updated AEFI guidelines are available in the hospital.
- Ensure all relevant health professionals are periodically trained on AEFI surveillance.
- Submit monthly AEFI surveillance reports to the program by the first week of the following month.
- Lead the hospital AEFI committee for serious AEFI or death investigation when required.
- Submit AEFI case investigation report to the program within 48 hours of notification.
- Analyse hospital surveillance data to assess trends and inform decision-making.
- Ensure timely management of cases and referrals when necessary.
- Support laboratory assessment if required.
- Ensure availability of emergency drugs, kits and medical equipment to manage AEFI in hospitals.
- Ensure adequate supervision and monitoring in the hospital.
- Sensitize and educate the community regarding AEFIs.

### 3.4.4 District Public Health Officer

- Establish a functional district AEFI committee with a clearly defined ToR.
- Ensure complete documentation of AEFI surveillance activities at all levels of health facilities.
- Ensure adequate availability of adequate AEFI reporting, case investigation , and death investigation forms in all the health centres.
- Ensure that updated or current AEFI guidelines are available in all health centres.
- Ensure that relevant health professionals are periodically trained on AEFI surveillance.
- Collate monthly zero-integrated VPD surveillance reports from health centres and submit them to the program by the first week of the following month.
- Support the district AEFI committee for serious AEFI or death investigation when required.
- Ensure AEFI case investigation reports are submitted to the program within 48 hours of notification.
- Ensure timely management of cases and referrals in consultation with CMO/MO.
- Support laboratory assessment if required.
- Ensure the availability of emergency drugs, kits, and medical equipment to manage AEFI in health centres.
- Analyse surveillance data at the district level to assess trends and inform decision- making.
- Provide adequate supervision and monitoring of health centres to ensure the proper handling of AEFI cases.
- Sensitize and educate the community regarding AEFIs.

### 3.4.5 Vaccine Preventable Disease Program

- Ensure a functional national AEFI committee with a well-defined ToR.
- Maintain and analyse AEFI surveillance data at the national level.
- Ensure all reported AEFI cases are documented in a national database, properly analysed, and used to support evidence-based decision-making.
- Monitor reported AEFI data for potential signals of unrecognized vaccine-related AEFI and recommend further investigation.
- Monitor the timeliness and completeness of AEFI reporting and provide targeted support to low-performing districts.
- Reinforce AEFI reporting from health centres and share quarterly feedback with relevant stakeholders.
- Support AEFI investigations at all levels as needed and conduct effective monitoring and supervision.
- After receiving the case investigation form, the program should assign an Epi number [PHC (AEFI) – indicates country and AEFI, followed by district code (use three alphabets), year (use last two digits and case number in two decimal places. Example: PHC (AEFI)-PAR-25-01 – 1$^{st}$ AEFI case from Paro investigated in 2025).
- Engage the national AEFI Committee for timely causality assessments.
- Coordinate with relevant stakeholders for biological sample referrals, testing, vaccine safety concerns, and product recalls when necessary.
- Plan and conduct periodic training and sensitization programs to strengthen reporting and investigation capacity for health professionals and AEFI committees.
- Disseminate causality assessment reports and recommendations to relevant stakeholders and communicate to the media, when appropriate and necessary.
- Activate the communication plan during any AEFI-related crisis.

- Conduct periodic monitoring and evaluation of the AEFI surveillance system to identify strengths, gaps, and areas for improvement.
- Share the AEFI reports with the BFDA.
- Maintain strict confidentiality and ensure ethical handling of all AEFI-related data, investigations, and communications.

#### 3.4.6 Bhutan Food and Drug Authority (BFDA)

- Collect, compile and maintain AEFI reports at the national level.
- Share AEFI reports to the global database.
- Make regulatory decisions on time.
- Share safety information on vaccines to relevant stakeholders.
- Facilitate the conduct of laboratory analysis of vaccines whenever required.
- Conduct regulatory inspection to ensure AEFI reports are shared with the Authority as per the relevant guidelines or procedures.
- Liaise with national or international organizations to generate safety information on vaccines.

### 3.5 National AEFI committee composition

The national AEFI committee should comprise of following members

- Medical specialist
- Microbiologist
- Public Health Specialist
- Paediatrician
- Pathologist,
- Pharmacist and
- Representatives from partner agencies can be co-opted members as and when required.
- The program officer should be the member secretary.

### 3.5.1 Responsibilities for National AEFI Committee

- Conduct causality assessments for serious AEFI cases using WHO recommended AEFI causality assessment methodology.
- Review and analyse AEFI case investigation reports on a quarterly basis., ensure the completeness and accuracy of submitted forms and supporting documents (e.g., medical records, test results).
- Identify and provide recommendations to NITAG for policy decisions.
- Provide guidance and technical support to AEFI subcommittees and health centres during investigations, as needed.
- Support the development, review and dissemination of training materials and guidelines on AEFI surveillance and management.
- Facilitate awareness campaigns to encourage reporting of AEFI cases from all health facilities.
- Assist in the development and implementation of strategies to strengthen the national AEFI surveillance system.
- Ensure confidentiality and ethical handling of all AEFI-related data and investigations.
- Conduct operational research to improve AEFI detection, investigation, and management.
- Undertake any additional responsibilities related to vaccine safety, as deemed necessary by the committee or the Ministry of Health.
- Serve as spokesperson during the serious AEFI incidents.

# CHAPTER 4: AEFI REPORTING

AEFI reporting is the first important step in AEFI surveillance. while the primary reporters are health professionals.parents/guardians may also report AEFIs. Suspicion of AEFI can also be reported.

## 4.1 Which event should be reported?

Any AEFI that raises concerns to parents or health professionals should be reported. In particular, health professionals must report the following cases specifically:

- Serious AEFI
- Signals and events associated with a newly introduced vaccine
- AEFI that may have been caused by an immunization error
- Of unexplained significant medical events occurring within 30 days after vaccination
- Events causing significant parental or community concern, including minor AEFI

## 4.2 When to report

- Reports must be made immediately to enable timely decision making to initiate investigations and interventions. For incidents with many cases or of community concern, AEFI should be reported through an urgent telephone call/email/other media.
- Any unexplained sudden death within 30 days of vaccination where no alternative cause of death can be established should be reported.
- Once a health professional detects an AEFI, it is important to ensure that the recipient has received the necessary treatment/management even before completing the reporting process.
- Reassure the affected recipient/parents/guardians that an investigation would be carried out and findings will be communicated.

### 4.3 How to report

- All serious and non-serious AEFI should be reported using the AEFI reporting form (Annexure I).

### 4.4 Who will report

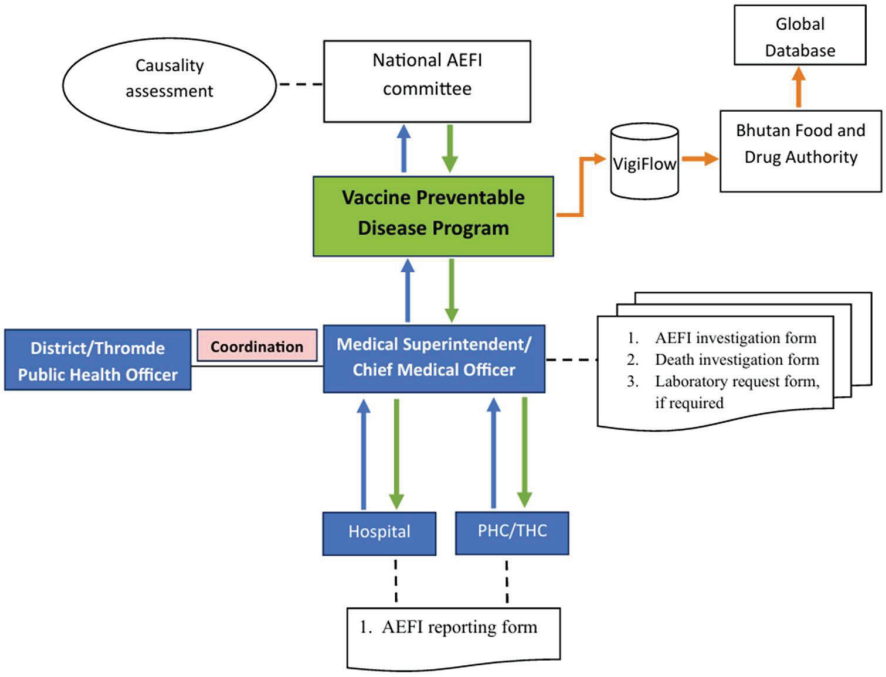
- All health professionals who have come in contact with AEFI cases must report AEFIs. The vaccine recipients, parents /guardians may also report suspected AEFIs.

### 4.5 Reporting AEFI during immunization campaigns

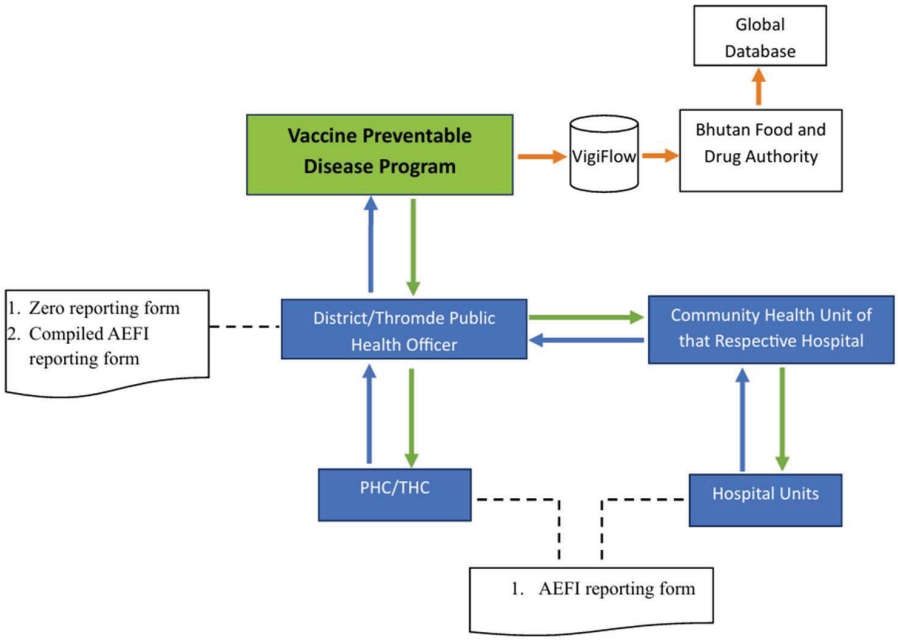
During mass immunization or a special immunization program, it is of utmost importance to ensure functional AEFI reporting for two reasons.

- Mass immunization and special immunization programs cover a large number of individuals in a particular target group over a short time frame. Therefore, a higher number of AEFI may occur within a short time period. Although the actual rate of events remains unchanged, the increased number of events tends to be noticed by both health professionals and the public, particularly when injectable vaccines are used and when there are periods of public outreach. Unless an event is properly investigated or analysed, it can cause concern among the public and may also affect the immunization program.
- During special immunization programs, a new vaccine may be introduced with no prior experience of, or little information on, adverse reactions. There is a possibility of detection of signals through enhancing surveillance during special immunization programs.

## Reporting of serious AEFI cases




## Reporting of minor AEFI cases from all health facilities, except JDWNRH



## Reporting of minor AEFI cases from JDWNRH

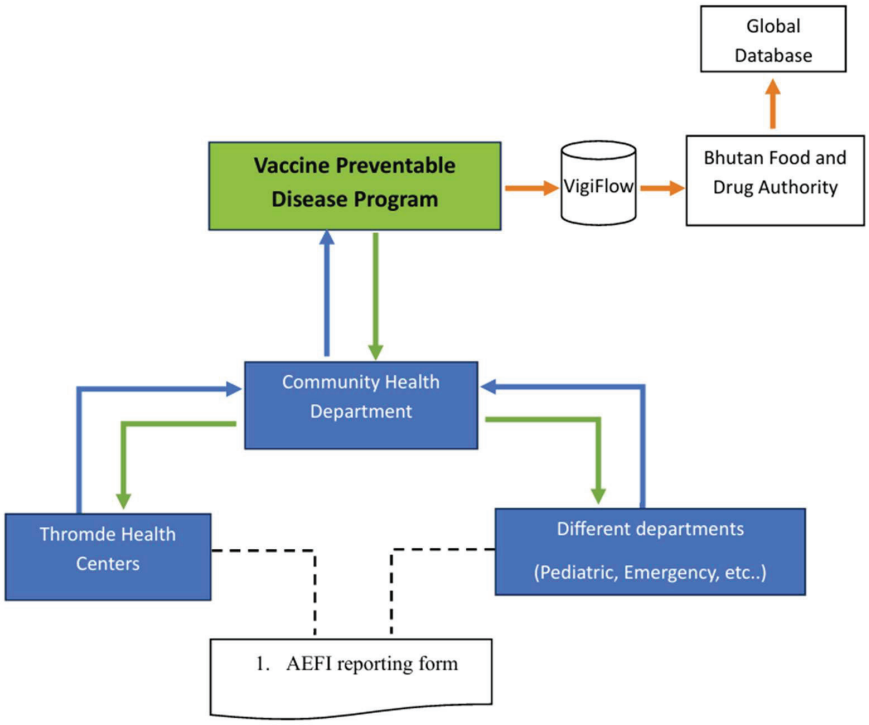



*Table 4.1: List of examples of reportable AEFI*

| Reportable AEFI | Time onset following immunization* |
|---|---|
| **Acute flaccid paralysis** | |
| • OPV recipient | 4-30 days following immunization |
| • Contact of OPV recipient | 4-75 days following immunization |
| Anaphylaxis (after any vaccine) | Within 48 hours of immunization |
| Brachial neuritis (after tetanus-containing vaccine) | 2-28 days following immunization |
| Disseminated BCG infection after BCG vaccine | Between 1 and 12 months |

| Reportable AEFI | Time onset following immunization* |
|---|---|
| **Encephalopathy** | |
| after measles/MMR vaccine | 6-12 days following immunization |
| after DTP vaccine | 0-2 days following immunization |
| Hypotonic hyporesponsive episode (HHE) after DTP/Pentavalent vaccine | Median time is 3-4 hours after immunization but ranges from immediate to 48 hours. However, it can occur even after 48 hours |
| Injection site abscess (bacterial/sterile) after any injectable vaccine | Not specific. However, commonly within first 14 days of immunization |
| • Lymphadenitis after BCG vaccine | |
| • Osteitis/osteomyelitis after BCG vaccine | Between 1 and 12 months |
| Persistent (more than 3 hours) inconsolable screaming after DTP/PvV vaccine | Common immediately and up to 48 hours of immunization. However, it can occur even after 48 hours |
| Sepsis (after any injectable vaccine) | Within 7 days following immunization |
| **Seizures, including febrile seizures** | |
| after measles/MMR | 6-12 days following immunization |
| after DTP/PvV | 0-2 days following immunization |
| Severe local reaction (after any injectable vaccine) | Within 7 days following immunization |
| Thrombocytopaenia (after measles/ MMR) | Median time is 12–25 days after immunization, but the range is 1-83 days |
| Toxic shock syndrome (TSS) (after any injectable vaccine) | Commonly within 72 hours following immunization |

| Reportable AEFI | Time onset following immunization* |
|---|---|
| Death, Hospitalization, Disability and any other severe and unusual events that are attributed to immunization by health workers or the public. | No time limit, but in general those within 30 days following any immunization. |

## 4.6 How can reporting be encouraged?

Health professionals should be encouraged to report AEFI without fear of penalty. AEFI should be reported, even if there is a delay in the submission of information by the health professionals. Reporters should receive timely feedback on the results of investigations and actions taken. This should be carried out at every level of the surveillance process and include positive reinforcements, such as an acknowledgement of reports received. FFeedback should also include sharing information on the management of AEFI, capacity development for the reporters, especially concerning future vaccination, and the outcome of investigations or causality assessments when these are carried out.

# CHAPTER 5: AEFI INVESTIGATION

The goal of the AEFI investigation is to determine the cause of an AEFI. If a programmatic error is found, 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 very act of investigation of the incident itself strengthens public confidence towards immunization.

## 5.1 Objectives of investigating AEFI cases

- To confirm the reported diagnosis or establish other possible diagnoses
- To review the details of the vaccine used, including its type, batch number, and storage/handling conditions, to assess any potential link to the AEFI
- To identify details of specifications of the vaccine used to immunize the affected recipient and any vaccine-related link for the given AEFI
- To examine the operational aspects of the program
- To determine whether a reported event was a single isolated incident or a cluster and find out the vaccine used
- To determine whether unvaccinated people are experiencing the same medical incidents

## 5.2 Basis of AEFI Investigation

There are many background factors/reasons involved in deciding whether an AEFI 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 the occurrence of signs and symptoms of a disease does not automatically suggest that the vaccine is the cause or aggravating or contributing factor. A thorough Systematic assessment of the patient and the relevant factors will determine the cause-and- effect relationship of the event. The basis of the investigation is to identify whether the AEFI is related to the vaccine or immunization error (programmatic error).

### 5.2.1 The factors to be considered for the investigation of AEFI

- Whether multiple cases occurred among recipients from the same clinic.
- Whether the unvaccinated population of the same age group presented with similar symptoms/events.
- Whether similar symptoms or occurrences were reported by other recipients of the same batch of vaccine.

*Table 5.1: Reasons for causing immunization error-related AEFI*

- Using incorrect vaccine(s), dose and/or diluent
- Reuse of reconstitution (diluents)/AD syringes
- Improper/unsafe preparation of vaccines including use of AD syringes in unsafe manner (failure to  follow] aseptic technique)
- Incorrect method of administration (route, site and technique)
- Improper storage of the AD syringes, diluents and droppers
- Substitution of vaccines or diluents with drugs or other substances
- Use of expired AD syringes, vaccines and diluents
- Use of contaminated vaccines or diluents
- Failure to verify the condition of the packaging that guarantees the sterility of AD syringes
- Improper storage of the vaccines (cold chain not maintained, other materials /drugs stored with vaccines)
- Failure to discard reconstituted vaccines or those past the recommended time, and using them in subsequent sessions.
- Failure to check or follow the Vaccine Vial Monitor (VVM) status before use.
- Ignoring known contraindications to vaccination)(e.g., re-administering Pentavalent vaccine to a child who had a previous severe reaction to it)
- Not following “open vial” policy criteria appropriately
- Use of thawed (suspected) frozen vaccines without carrying out shake test
- Administering vaccine doses at invalid time interval (<28 days)

### 5.2.2 The factors to be considered during AEFI investigation

- Determine if the Frequency of occurrence (common/rare/not previously reported) - occurs within the expected frequency range.
- Assess whether the reported incident is a known reaction to the vaccine.
- Determine if similar events were reported among unvaccinated populations.
- Evaluate whether the Event can be plausibly/probably explained by the biological properties of the vaccine.
- Significant temporal relationship between the event and immunization.
- History of similar events; related to or independent of vaccination.
- History of drug therapy; concomitant/previous.
- Concomitant or preceding medical condition which could explain the event (immune- compromised status of the recipient).
- Any other factors that could explain the events, eg, Immunization error.

## 5.3 AEFI Requiring Investigation

- All serious AEFIs must be investigated
- Life-threatening events (e.g., bacterial abscess, severe local reaction, sepsis, BCG lymphadenitis, anaphylaxis, toxic shock syndrome) or that result in hospitalization, disability, congenital defect or death.
- Cluster AEFI
- AEFI that may have been caused by immunization error
- Events causing significant parental or community concern

## 5.4 When should an investigation take place?

Investigation should be immediately conducted following notification if deemed necessary to determine the cause as early as possible.

## 5.5 How should an investigation take place?

All serious AEFI should be investigated by the district/hospital AEFI team. In case of death, a paediatrician/medical specialist should be included in the team as recommended by the National AEFI Committee. After the investigation, the investigating team should present the findings to the national AEFI committee. If the event is of national concern based on the report sent by the investigation team, a team from the national AFEI committee should conduct the investigation.

For both minor and serious AEFI, the health professionals must notify DHO/MS using an AEFI reporting form (Annexure I).

*Table 5.2: Composition of AEFI investigation team*

| At National level | At District/Regional hospital level |
|---|---|
| • Clinician<br>• Pharmacist<br>• Public Health Specialist<br>• Laboratory personnel<br>• Other health officials if deemed necessary | • Clinician (In case of death, preferably a paediatrician/medical specialist should be involved from the nearest RRH)<br>• DHO/MS<br>• MCH In-charge<br>• Pharmacist<br>• Laboratory personnel |

### 5.5.1 Preparation and Planning for Investigation

Investigation should be coordinated by the District/Regional AEFI committee. The team should be led by MS/CMO in coordination with the DPHO/TPHO. The MS/CM0 will be responsible for the following:

- Provide an overview of the case.
- Review the AEFI reporting form and any other data.
- Collect information from local health centres
- Inform health centres about the planned investigation visits.
- Provide the team with the necessary logistical support, including investigation materials

### 5.5.2 Conducting the investigation

- Introduce the team to health centres and inform them of the objectives of the investigation and planned activities
- Review background information on the previous AEFI reported from the health centre to establish context and identify patterns or recurring issues.
- Simultaneously conduct investigations using the AEFI Investigation form (Annexure II)
- Collect relevant samples for further investigation as required
- The case investigation should be completed within 72 hours of case notification.

### 5.5.3 Information to be obtained during the investigation

- Collect medical history of the vaccine recipients
- Verify and confirm if the patient had received the suspected vaccine, concurrently any other vaccines or drugs
- Observe the immunization sessions, cold chain monitoring and vaccine management
- Inquire about similar events in an unvaccinated population
- Seek information from other recipients/communities regarding any similar events

## 5.6 Death Investigation

- In the event of a death following immunization, the field investigation has to be initiated immediately by the district AEFI team with the help of the national AEFI committee, if required.
- Information should be obtained using the standard death investigation form (Annexure II) and any additional information if necessary.
- In the event where the deceased's party refuses to be investigated, ensure their decision is respected and well documented, signed by the investigation team

- Observe the immunization sessions, cold chain monitoring and vaccine management
- Information on similar events among other recipients of vaccines in the same health centre and the district.
- Where applicable and possible, involve a forensic specialist.

## 5.7 Investigation of clustered AEFI cases

A cluster of AEFI is defined as two or more cases of the same AEFI related in time, place or vaccine administration. The exact nature of the relationship between the adverse events (e.g., duration of time, proximity of place) will differ by the nature of the events and the circumstances in which they occur. Investigation of a cluster should follow the same algorithm (Flow chart) shown in Figure 5.1 with the following steps.

i. Establishment of a case definition, if it is not defined yet
ii. Identification of all vaccinated and unvaccinated populations who meet the case definition
iii. Obtaining immunization history (when, where and which vaccines were given)
iv. Identification of any other common exposures of the cases

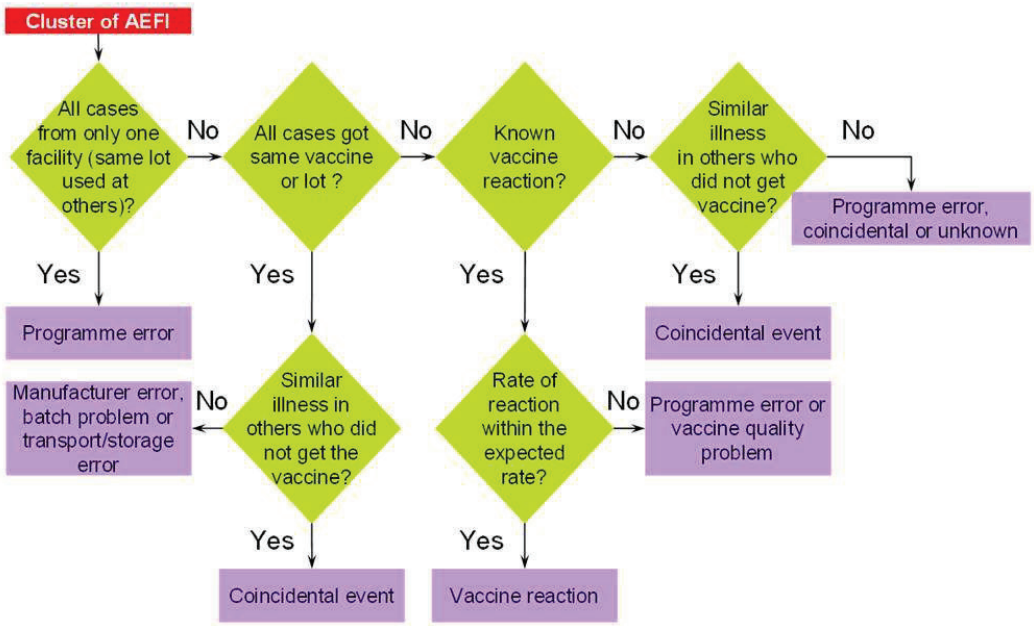



*Figure 5.1: Algorithm used in identifying the cause of AEFI in cluster cases*

- If all AEFI cases are linked to the same health professionals/ immunization clinic and there are no other cases from other clinics, **Programmatic/ Immunization error is likely.**
- If all cases received the same vaccine or lot from different clinics and there are no similar cases in the general community, **a problem with the vaccine, vaccine defect is likely.**
- If the event is a known vaccine reaction but occurring at an increased rate, **Programmatic error or a vaccine defect are likely the causes.**
- If cases include people in the same area in the same age group who were not immunized, **a coincidental event is likel**y.

# CHAPTER 6: LABORATORY INVESTIGATIONS OF AEFI

Laboratory testing can help confirm or exclude the suspected cause. However, the routine testing of samples is not mandatory following AEFI, particularly if the cause is evident, such as a coincidental event or an immunization error. Laboratory testing is always costly; therefore, it should be requested based on clear suspicion and not as a routine procedure. Lab testing should never be conducted before a working hypothesis has been formulated. Responsibilities to make decisions on the collection of samples should be carried out by a person(s) or agent(s) as shown in Table 6.1. The Laboratory request form (LRF) is given in Annexure IV.

*Table 6.1: Activities and responsibilities for specimen collection*

| Activity | Responsibility |
|---|---|
| Decision to collect sample (samples should be collected immediately and sent if the National AEFI committee decides to) | • District AEFI Team<br>• Drug inspector |
| Decision on type of samples that need to be collected | • National AEFI committee<br>• Drug Inspector<br>• RCDC |
| Collection and sending of samples | • Drug Inspector<br>• RCDC/hospital laboratory |
| Packaging & Cold Chain maintenance of samples | • Drug Inspector<br>• RCDC/hospital laboratory |
| Sealing of specimen using “official lac seal” | • Drug Inspector |
| Transportation of samples to laboratories | • Drug inspector<br>• Hospital laboratory |
| Laboratory for testing specimen | • RCDC<br>• RCDC-identified laboratories |

| Activity | Responsibility |
|---|---|
| Funding | • Ministry of Health |
| Reporting and sharing of laboratory results | • RCDC will forward a copy of the report to VPDP and BFDA, Ministry of Health.<br>• Ministry of Health will share the report to other relevant stakeholders |

## 6.1 Laboratory testing of vaccines and logistics

Adequate quantities of the implicated vaccine/diluent samples should be collected from the site of occurrence of AEFI and the last vaccine storage point. The same should be shipped in a cold chain to RCDC immediately. Determination of what samples to test, if any, depends on the working hypothesis for the cause of the event shown in Table 6.2.

Four sealed sets of samples with equal quantities should be prepared; 1 to be sent to RCDC, 1 to be retained at the site of collection (health centre or EPI store), and 2 sets to be retained with the drug inspector. The quantity of vaccine and diluent sample to be collected is shown in Table 6.3.

*Table 6.2: Laboratory testing to investigate AEFI by working hypothesis*

| Working Hypothesis | Specimens to Send | Laboratory Test |
|---|---|---|
| Vaccine transportation or storage | Vaccine vial | Visual test for clarity, presence of foreign matter, turbulence, discoloration or flocculation (examine under magnification) |
| Reconstitution error | Vaccine vial and/or diluents | Chemical composition analysis for abnormal components (e.g. suspect medicine used instead of vaccine or diluent), |

| Working Hypothesis | Specimens to Send | Laboratory Test |
|---|---|---|
| Non-sterile injection | Needle, syringe, vaccine vial and diluents | Sterility, if an infectious cause is suspected |
| Vaccine problem | Vaccine vial | Chemical composition analysis: preservatives, adjuvant level, etc. (e.g. aluminium content) or biological tests for foreign substances or toxins if abnormal toxicity is suspected |

*Table 6.3: Quantity of implicated vaccine/diluents to be collected*

| Item | Specimens to Send | | Laboratory Test | |
|---|---|---|---|---|
| Vaccine | Unused vaccine vials / ampoule | Unused diluent/ ampoule | Unused vaccine vials/ampoules (one fourth of total samples collected) | Unused diluent vials/ampoules (one fourth of total samples collected) |
| DTP group of vaccines (including Pentavalent) | 01 dose X 120 vials | NA | 01 dose X 30 vials | NA |
| BCG Vaccine | 20 dose X 160 vials | 160 diluents | 10 dose X 40 vials | 40 diluents |
| | | 160 diluents | 20 dose X 40 vials | 40 diluents |
| Oral Polio Vaccines | 20 dose X 40 vials | NA | 20 dose X 10 vials | NA |

| Item | Specimens to Send | | Laboratory Test | |
|---|---|---|---|---|
| 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 |
| 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 |

On the receipt of adequate samples with proper and complete documentation, the National Drug Testing Laboratory (NDTL), RCDC, shall coordinate with BFDA and WHO-accredited laboratories are responsible for testing of vaccines and diluents for physical aspects, sterility, abnormal toxicity and biochemical identity. Once the test results are received, RCDC will officially submit the test results to BFDA and VPDP, MoH.

## 6.2 Laboratory testing of biological specimens

The type of specimen required in each situation will depend on the symptoms and signs of the patient and the clinical decisions made by the doctor in charge of the case. Table 6.4 gives a general outline of some of the specimens that could be collected.

*Table 6.4: Guide to human specimen sample collection following selected AEFI*

| Hypothesis | Specimen | Purpose | Specimen collection |
|---|---|---|---|
| Suspected bacterial sepsis due to contaminated vial, needle contamination, coincidental | Whole blood | Bacterial culture | Blood 8-10 mL in each of 2 blood culture bottles |
| | CSF | Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other) | Sterile container Viral culture media |
| Suspected viraemia due to vaccine virus or coincidental disease | Serum | IgM and IgG antibodies for viral pathogens | Clotted blood 5-10 ml |
| | CSF | Differential cell count, biochemistry, bacterial and viral culture, PCR (HSV1/2, enterovirus, other) | Sterile container Viral culture media |
| | Skin Vesicle | Viral culture | Sterile container Viral culture media |

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

### 6.2.1 Key Points

- Laboratory testing is not a routine requirement but may be a part of an investigation.
- Laboratory testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood, etc.) is important because it may be required later in the investigation.
- Therefore, proper storage and transportation of these suspected samples must be ensured to maintain their integrity for accurate testing.

# CHAPTER 7: ANALYSIS OF AEFI DATA

Data analysis is a process of collecting, transforming, cleaning and modelling of the data to discover the required information(s). It supports researchers/investigators to identify problems, generate hypotheses and help in decision-making.

## 7.1 Analysis of data on AEFI depends on the following components

- Completeness and timeliness (reporting and case investigation of serious AEFI) of submitted AEFI forms
- Verification and validation of data accuracy
- Identify health centers where AEFI cases are not reported and determine the reason(s), which could be either of the following:
  - » No AEFI cases occured
- Failure to report despite the occurrence of case(s)
- Checking on “zero reporting”
- Assessing AEFI reports received during stipulated periods
- Assessing the number of events and rates for 1000, 10,000 or 100,000 doses of particular vaccines used
- Categorising the AEFI by type.
- Analysing type of immunization errors by numbers and rates per 1000, 10,000 or 100,000 doses of particular vaccines used
- Comparison of the observed rates with available or known vaccine reaction rates

## 7.2 Analysis and Interpretation of Data

### 7.2.1 Step 1 - All reported AEFI data should be line-listed

- Line listing of Reporting forms will help with the initial identification of clustering, and any unusual or significant reporting events based on time, person and place that will require further analysis.

### 7.2.2 Step 2 - Tabulate AEFI data by place, person, time, antigens and type of events (e.g: high fever, abscess)

- This further filters the AEFI cases by different variables and helps the program managers to generate hypotheses for further analysis.
- At this step, it is also possible to identify common immunization errors

(an increased number of abscess cases from one immunization centre). However, further investigation of such observation is necessary to confirm the causality.

### 7.2.3 Step 3 - Calculate AEFI rates

- The number of doses administered for each antigen serves as the denominator for calculating reported AEFI rates for each antigen in a given time (by month, quarter or year).
- The analysis should expand to the AEFI rates by first, second or third dose when the antigen is administered multiple times. In this case the denominator should be the number of doses administered for each specific dose(1st, 2nd or 3rd doses) that needs to be used as the denominator.

For example, if the number of children under 1 year of the population is 5000. The coverage of MMR vaccine is 90%. During the same year, 20 febrile seizures were reported following MMR vaccination. To calculate the rate of febrile seizures:

The numerator for this vaccine reaction (febrile seizures) is 20.

*The denominator is the number of doses of MMR used X (100, 1000, 10,000, 100,000) 20/(0.90 X 5000) X 100=0.44% (for common and minor AEFIs/ local level)*

*20/(0.90 X 5000) X 1000=4.44 per 1000 <5population (for serious AEFI/at national level)*

## 7.3 Who should do the data analysis

Data analysis should be carried out at different levels of health centres and districts within the capacity of the health professionals, as shown in Table 7.1.

*Table 7.1: Data analysis at different levels of health facilities and its significance*

| Health facility level | Data to be analysed | Importance of data analysis at given level |
|---|---|---|
| Sub-post / PHC/ District / Referral hospital | Number of reports by clinics, ORCs by a given time Reported AEFI by place (PHC, Sub-post & ORCs), persons & time, Cluster analysis Reported AEFI by antigen type | These are the important indicators (timeliness, completeness) at the PHC and Sub-post level.<br><br>Will be able to identify if the reactions are due to vaccines, immunization errors or a coincidence.<br><br>Identification of immunization errors will lead to corrective action. |
| National level VPDP / MoH | Number of reports from all levels Reported AEFIs by place (clinics, hospitals), persons & time Cluster analysis | These are program operation indicators (timeliness, completeness) at the intermediate/national level.<br>Cluster analysis will lead to the identification of immunization errors, coincidence and vaccine reactions. Will be able to identify vaccine reactions, including signal detection.<br>• Leads to taking operational and policy decisions at the national level |

**Data analysis should be carried out annually at every health facility (form to be developed); for their understanding and planning*

### 7.4 Determining the cause of AEFI

- For a few medical events, the diagnosis itself will show the cause, whether it is program-related, vaccine-induced, coincidental or an injection reaction. In others, external evidence may be required to identify the cause. Later, it will be possible to analyse the data and assign a cause and then to further classify it into one of the recognized categories of AEFI.
- Recommendations should be made depending on the findings and conclusion of the investigation. It should include the action that needs to be taken to remedy the identified problem. Action should be taken by the program managers, district health authority and at all levels of health centres.

## CHAPTER 8: CAUSALITY ASSESSMENT OF AEFI

Causality assessment is the systematic evaluation of the information obtained on AEFI to determine the likelihood that the event might have been caused by the vaccine. Causality assessment does not necessarily establish whether or not a definite relationship exists but generally ascertains a degree of association between the reported AEFI and the vaccine/vaccination process. Causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization program among the health sector and the public. It provides a more objective explanation and facilitates better management of the AEFI. It also helps to define the safety profile of the concerned vaccines. Therefore, determining whether or not an AEFI is attributed to the vaccine or vaccination process decides the steps needed to be taken to address the event.

### 8.1 Importance of Causality Assessment

- To identify vaccine-related problems
- To identify immunization error-related problem
- To exclude coincidental events
- To detect signals for potential follow-up, testing of hypothesis and research

- To validate pre-marketing safety data with comparison to the post-marketing surveillance safety data.

## 8.2 Factors affecting the quality of causality assessment

- Performance of the AEFI reporting system in terms of quality of case reporting and follow-up investigation
- Availability of adequate medical information, clinical investigations and follow-up on cases.
- Quality of the causality review process, including access to appropriate expertise.
- Inadequate or incomplete case information leads to the case becoming ineligible for causality assessment or considered unclassifiable due to a lack of crucial information.
- Even with reasonably complete information, the relation of a vaccine to the reported AEFI may at times be indeterminate due to insufficent clear evidence of a causal link, conflicting external evidence, and other inconsistencies.

**However even if the information is incomplete, it should be recorded because reporting more cases may lead to a stronger signal detection and a plausible hypothesis of any link.*

## 8.3 The causality assessment process should be performed by a team of

- Paediatrician
- Epidemiologist
- Clinical pharmacist
- Forensic medicine/pathologist.

All members of the team should have received formal training in the process of causality assessment. In addition, experts from other specialities may be involved for the causality assessment of specific events when necessary. The committee needs to be independent and work in close collaboration

with the immunization program and the BFDA. The program should not be involved in the causality assessment procedure, except to ensure that all the cases submitted for causality assessment are complete and include all necessary records.

## 8.4 Causality assessment should be performed in the following cases

- All Serious AEFI
- Clusters of events above an expected rate or level of severity
- Signals generated as a result of an unusual individual case or a cluster of cases
- AEFI that may have been caused by immunization error
- Significant medical events of unexplained cause occurring within 30 days after a vaccination
- AEFI not listed in the product label
- AEFI that are causing significant parental or community concern

## 8.5 Steps to be taken before starting a causality assessment

### 8.5.1 Three prerequisites before conducting a causality assessment are

- The AEFI case investigation should be completed. Incomplete investigations could mislead the classification of the event. When an investigation is incomplete, follow-up efforts to obtain additional information and documents should be made.
- All relevant details of the case should be available at the time of assessment. Details should include documents about the investigation as well as laboratory and autopsy findings where appropriate.
- There must be a “diagnosis” using standard or widely accepted criteria for the adverse event, clinical sign, abnormal laboratory finding, symptom or disease in question.

## 8.6 Criteria for establishing causality

The Bradford-Hill criteria will provide a structured approach to assess the association and test the hypotheses during the causality assessment.

### 8.6.1 Criteria (Evidence) for establishing causality

**i. Strength of the association**

The stronger the association, the more likely that the relation is causally associated.

**ii. Consistency of the association**

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

**iii. Specificity of the association**

The vaccine is the only known cause of the event.

**iv. Temporal sequence**

Exposure to the vaccine must precede the occurrence of the event; this is the only absolutely essential criterion for causality.

**v. Biologic plausibility**

Biological plausibility may provide support for or against vaccine causality. The association should be compatible with existing theory and knowledge related to how the vaccine works.

**vi. Definitive proof that the vaccine caused the event**

There is clinical or laboratory proof that the vaccine caused the event.

**vii. Prior evidence that the vaccine in question could cause a similar event**

The concept of "re-challenge" is more commonly used in causality assessment of drugs, but it has also been helpful for certain vaccine-event considerations (e.g. Guillain-Barre. syndrome occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine).

## 8.7 Methods of performing Causality assessment

The worksheet used for the causality assessment of an individual AEFI case is presented in Annexure V. This can be used by the reviewers to decide on causality. The WHO has also developed an e-tool that will help to perform an AEFI causality assessment. Details are available at https://gvsi-aefi-tools.org/ . When multiple vaccines are given simultaneously, the reviewers will have to assess causality for each suspected vaccine individually. There are four steps involved in causality assessment.

### 8.7.1 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. Before proceeding with causality assessment, it is necessary to confirm that the vaccine was administered before the event occurred. Use the existing case definition for the causality assessment, but if it doesn't, refer to the Brighton Collaboration accessible at https://brightoncollaboration.org/public, and standard medical literature or national guidelines. If the reported AEFI does not have a valid diagnosis, the AEFI cannot be classified, and additional information should be collected to arrive at a valid diagnosis. Figure 8.1 shows the process involved in identifying eligibility for causality assessment.

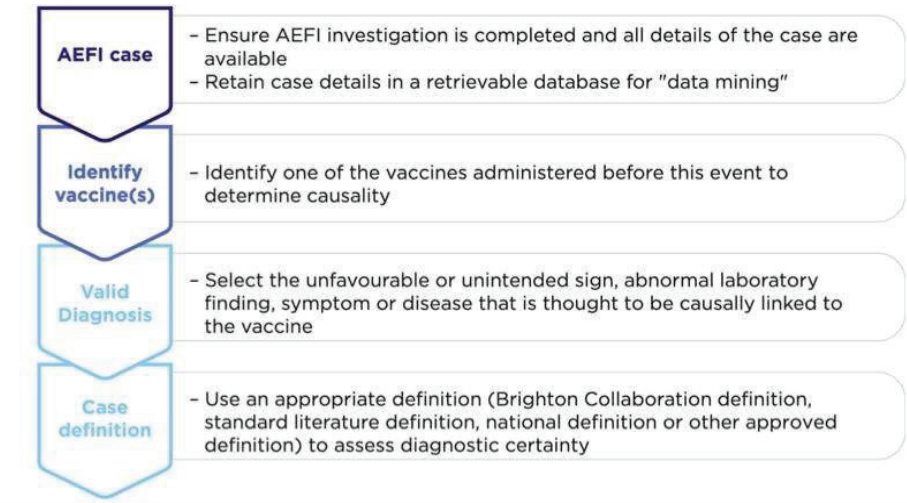



*Figure 8.1: Causality assessment - Eligibility*

At this stage, it is also essential for the assessor to define the "causality question," as shown in Figure 8.2.

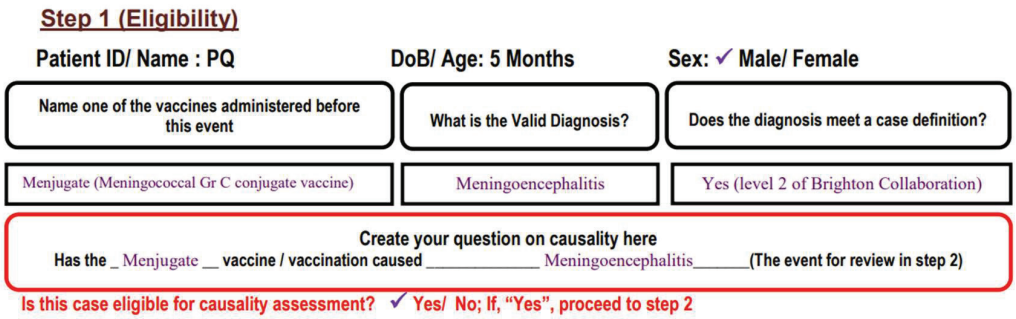



*Figure 8.2: Develop questions on vaccine-event causal association*

Examples of causality questions are as follows:

- "Has the vaccine A caused hepatomegaly?" (eg: an unfavourable or unintended sign)
- "Has the vaccine B caused thrombocytopenia?" (eg: laboratory findings)
- "Has the patient complained that the vaccine C caused itching?" (eg: symptoms)

- "Has the vaccine D caused meningitis?" (eg: a disease)

It is important that, if an AEFI is reported and does not meet the eligibility criteria, attempts should be made to collect additional information to ensure that the criteria are met. AEFI cases where the causality question cannot be created by an assessor are categorised as "ineligible". All cases reported, including ineligible cases, should be stored in a repository (preferably electronic) so that they can be accessed when additional information becomes available through reports of similar cases or periodic data mining.

For a given assessment, only one valid diagnosis and one vaccine administered can be assessed at one time. If multiple vaccines are administered to the patient at the same time, each vaccine should be assessed separately; when faced with multiple presumptive diagnoses, the assessor should consider doing a separate causality assessment for each diagnosis. Likewise, for a cluster of AEFI, each case must be assessed separately.

### 8.7.2 Step 2 - Checklist

- The checklist contains questionnaires to guide the assessor to collate the evidence needed for case review. It is designed to assemble information on the patient- immunization-AEFI relationship in the following key areas, as reflected in Figure 8.3.
- Once the checklist is systematically completed, the answers in the checklist are applied to the algorithm in Figure 8.4
- It is essential that all questions in the checklist be answered with any one of the options, "Yes", "No", "Unknown" or "Not applicable".
- When there is a positive response to any question, ("Yes" response), it is essential to provide an explanation for the positive response in the corresponding row under remarks. It will be observed that sometimes explanations for other responses "No", "Unknown" or "Not applicable" are also important to determine causality: therefore it is essential that the "Remarks" column is used to provide a detailed explanation on the reasons.

**Step 2 (Event Checklist) ✓ (check) all boxes that apply**

| I. Is there strong evidence for other causes? | Y N UK NA | Remarks |
|---|---|---|
| 1. In this patient, does the medical history, clinical examination and/ or investigations, **confirm** another cause for the event? | ☑ ☐ ☐ ☐ | *Yes – CSF PCR positive for herpes simplex virus* |
| **II. Is there a known causal association with the vaccine or vaccination?** | | |
| ***Vaccine product*** | | |
| 1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly? | ☐ ☑ ☐ ☐ | *Unknown – not reported so far in literature* |
| 2. Is there a biological plausibility that this vaccine could cause such an event? | ☐ ☐ ☑ ☐ | *Contains inactivated extracts of Neisseria meningitidis group C bacteria* |
| 3. In this patient, did a specific test demonstrate the causal role of the vaccine ? | ☐ ☑ ☐ ☐ | *No – CSF PCR positive for herpes simplex virus* |
| ***Vaccine quality*** | | |
| 4. Could the vaccine given to this patient have a quality defect or is substandard or falsified? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| ***Immunization error*** | | |
| 5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| 6. In this patient, was the vaccine (or diluent) administered in an unsterile manner? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| 7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| 8. When this patient was vaccinated, was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| 9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| 10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)? | ☐ ☑ ☐ ☐ | *As per investigation report* |
| ***Immunization anxiety (Immunization Triggered Stress Response - ITSR)*** | | |
| 11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation or anxiety)? | ☐ ☑ ☐ ☐ | *Anxiety cannot cause Meningoencephalitis* |
| **II (time). If "yes" to any question in II, was the event within the time window of increased risk?** | | |
| 12. In this patient, did the event occur within a plausible time window after vaccine administration? | ☐ ☐ ☐ ☑ | *Because there are no, "Yes" responses in II.* |
| **III. Is there strong evidence against a causal association?** | | |
| 1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event? | ☐ ☐ ☑ ☐ | *Unknown – hasn't been studied* |
| **IV. Other qualifying factors for classification** | | |
| 1. In this patient, did such an event occur in the past after administration of a similar vaccine? | ☐ ☑ ☐ ☐ | *Child fine after first dose* |
| 2. In this patient did such an event occur in the past independent of vaccination? | ☐ ☑ ☐ ☐ | *Was in good health previously* |
| 3. Could the current event have occurred in this patient without vaccination (background rate)? | ☑ ☐ ☐ ☐ | *Several causes for infant meningoencephalitis* |
| 4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event? | ☐ ☐ ☑ ☐ | |
| 5. Was this patient taking any medication prior to the vaccination? | ☐ ☐ ☑ ☐ | *"No" is also ok here* |
| 6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)? | ☐ ☐ ☑ ☐ | |

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

*Figure 8.3: Develop questions on vaccine-event causal association*

### 8.7.3 Step 3 - Algorithm

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

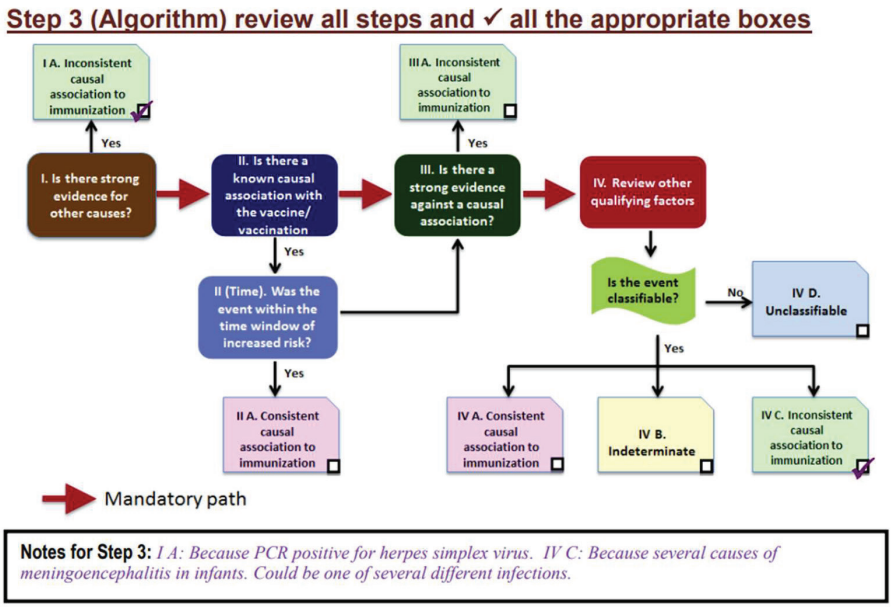



*Figure 8.4: Algorithm to determine AEFI classification*

### 8.7.4 Step 4 - Classification

The final classification is based on the availability of adequate information in Figure 8.5.

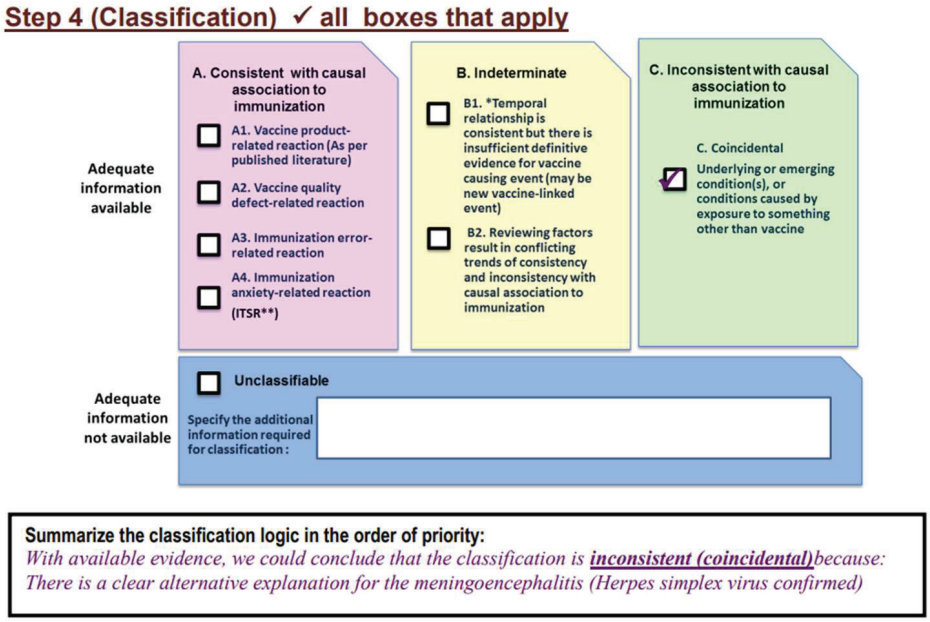



*Figure 8.5: AEFI classification chart*

## 8.8 Action to be taken after causality assessment

### 8.8.1 A. Consistent causal association to immunization

**i. Vaccine product-related reaction**

It is necessary to follow up with BFDA and vaccine suppliers.

**ii. Vaccine quality defect-related reaction**

If this reaction is related to a particular lot or batch, its distribution must be traced. Clear and specific instructions must be provided regarding whether the lot or batch should be used continuously. The BFDA and the marketing authorization holder must be informed about the AEFI.

**iii. Immunization error-related reaction**

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

**iv. Immunization anxiety-related reaction**

Vaccination should be administered in a calm, reassuring and safe environment.

### 8.8.2 B. Indeterminate

**i. Consistent temporal relationship but insufficient evidence for causality**

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

**ii. Conflicting trends of consistency and inconsistency with causality**

These cases are classified based on available evidence. If additional information becomes available, the case can be reclassified to a more definitive category. During the assessment, the reviewers should clarify what additional information would be helpful to finalize the causality assessment and should seek information and expertise from national or international resources.

### 8.8.3 C. Inconsistent causal association to immunization (coincidental)

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

# CHAPTER 9: FOLLOW-UP

Responding to AEFI may involve immediate short-term activities and long-term follow- up activities. These Follow-up activities should be based on findings of investigations, causality assessments and recommendations by the National AEFI committees.

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

## 9.1 Patient Care

It is of utmost importance to ensure that proper and early treatment is received by affected vaccine recipients, regardless of the diagnosis. Mild symptoms such as mild fever and pain are likely to be of self limiting and can be managed by reassuring and educating parents or care-givers during immunization. Health professionals must be trained to recognize AEFI, provide appropriate initial treatment or refer the case to higher level facilities when necessary. All AEFI must be reported as discussed earlier.

## 9.2 Corrective Actions

When the investigation is completed and the cause of AEFI is identified, it should be categorized appropriately. Based on the category, relevant corrective actions should be taken as indicated in the table.
Table 9.1 illustrates some corrective action to be taken after investigating AEFI.

*Table 9.1: Corrective actions to be taken after investigating AEFI*

| Type of AEFI | Follow-up action |
|---|---|
| Vaccine-related reaction | If there is a higher reaction rate than expected from a specific vaccine or lot, obtain information from the manufacturer and consult with the WHO regional office to consider: withdrawing that lot; investigating with the manufacturer; obtaining a vaccine from a different manufacturer. |
| Immunization error- related reaction | Correct the cause of the error. This may mean one or more of the following: changing logistics for supplying the vaccine; changing procedures at the health facility; training of health workers; intensifying supervision.<br><br>Whatever action is taken, it is important to review at a later date to check that the immunization error-related events have been corrected. |
| Coincidental | The main objective is to present the evidence showing that there is no indication that the AEFI is a vaccine-related reaction or immunization-error- related reaction and that the most likely explanation is a temporal association between the event and vaccine/vaccination. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to ensure that the event was truly coincidental.<br><br>The potential for coincidental events to harm the immunization program through false attribution is immense. |

## 9.3 Training and Awareness

The occurrence of AEFI is an opportunity for training and providing awareness to health professionals. Irrespective of the type or outcome of AEFI, it can be used to update knowledge, develop skills and build confidence among the health care workers. Awareness initiatives can expand to involve all

stakeholders linked to the immunization program, such as academia, teachers, volunteers, policymakers, politicians and the media.

## 9.4 Communication / sharing AEFI information

Communication and training are two important follow-up actions that have long-term impacts. They should not necessarily be limited to an individual event, but should emphasize the need for program managers and others involved in immunization to improve vigilance.

Transparent communication of vaccine safety data is essential to maintaining trust and ensuring the effective operation of the national immunization program. Accurate information must be shared with all relevant stakeholders to prevent misinformation and build public confidence. This can be done in two stages: sharing preliminary information at the initial stage of investigation and final data/ report after completion of the investigation and or causality assessment at a later stage.

## 9.5 Communication/Sharing AEFI Information with Media

The media plays an important role in disseminating information and in developing public awareness. Effective engagement with the media is essential to ensure accurate reporting, maintain public trust, and support the smooth functioning of the national immunization program.

Vaccine safety information should be shared with media stakeholders at two key stages:

1. **Preliminary Stage:** Early, verified information may be shared during the initial phase of the investigation.
2. **Final Stage:** Complete findings and final reports should be communicated after the investigation and causality assessment are concluded.

## 9.6 Media Management when an AEFI has occurred

When a serious AEFI occurs, it is critical to conduct a thorough investigation to determine causality.Media outlets may report on these events before full verification, potentially affecting public confidence in immunization services.

For this reason, the immunization program must ensure that accurate and timely preliminary information is available to share with the media.

Key principles for media management include:

1. Communicate clearly, cautiously, and factually.
2. Avoid speculation; share only confirmed and verifiable information.
3. Ensure designated spokespersons are trained and well-informed.

## 9.7 Monitoring Media

When there are AEFI cases, substantive inaccuracies can be spread by the media. This can include exaggeration on the number of AEFI cases, the gravity of the case, allegations of negligence, or rumours about vaccine procurement. The AEFI committee should act 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:

- Analyse rumour, its level, and its potential to cause damage.
- Anticipate how situations might evolve following the 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 for future information.
- If the rumour 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 program goals. · Plan how to prevent future rumours.
- The Ministry of Health should also immediately share adequate information and facts through the Ministry's page to maintain public confidence.

## 9.8 Preparing Message

The best messages get to the heart of the problem without lengthy explanations. During media interactions, aim to convey one central message that your audience will remember-even if they forget everything 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.

## 9.9 Preparing 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 a 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 at a defined time period.
- Reference to any relevant publication, video material or website.
    - » Spokesperson's details.
    - » Limited to one page of matter (400-500 words max).
    - » Short sentences (not exceeding two lines).
    - » Key message(s) are repeated.

## 9.10 Monitoring and feedback

Ongoing feedback and monitoring are essential for the success of AEFI surveillance, Provide bi-annual feedback reports to healthcare providers and stakeholders. This fosters a culture of participation and transparency. Use feedback to acknowledge reporting efforts, encourage continuous engagement, and inform training or corrective actions.
The AEFI surveillance system should be regularly reviewed at all levels to ensure that it is effective.

### 9.10.1 Monitoring and feedback includes

- Number of AEFI reports, categorized by type of reaction and vaccine(s) and causality assessment (with denominator data on the number of doses of vaccine given).
- Rate of each adverse event listed by individual vaccine (and lot number) nationally and by region · Unusual or unusually severe events or large clusters.
- Summary of other important/unusual investigations.
- Some of the key indicators that would help to monitor the system are: timeliness of reporting, investigation and causality assessments performed, and completeness and accuracy of submitted AEFI reports.
- Percent of routine reports (zero reports) received on time.
- Percent of AEFI cases listed.
- The percentage of serious AEFI detection, investigation, analysis and causality assessment conducted.

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# ANNEXURES

## 1.1 Annexure I: AEFI Reporting Form (Health Centres to MS/CMO/ DPHO then to VPDP)

| Patient Information: Name: | | | Date of birth: | | | Sex: |
|---|---|---|---|---|---|---|
| Name & Address of the Parent/Guardian & Mobile Nos:<br><br>CID: | | | | | | |
| **Information on the vaccine** | | | | | | |
| Name of Vaccine Received | Date of vaccination | Time of vaccination | Dose | Batch/ Lot Number | Expiry date | VVM Status (I, II, III, IV) |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| **Diluent Used: ☐ No ☐ if 'yes', Diluent batch lot number:**<br><br>**Expiry date of Diluent:** | | | | | | |
| **Place of vaccination: Hosp. ☐ PHC ☐ ORC ☐ School ☐ Others ☐**<br><br>**Date** | | | | | | |
| **Adverse Events: Date and Time of AEFI reported:**<br><br>**Date and Time when AEFI started:** | | | | | | |
| Local Adverse Events Requiring investigation<br>Yes ☐ No ☐ | | | Injection site abscess ☐ BCG Lymphadenitis ☐<br>Severe local reaction ☐ | | | |
| CNS Adverse Events Requiring investigation<br>Yes ☐ No ☐ | | | Vaccine associated paralytic poliomyelitis ☐<br>GBS ☐ Encephalopathy ☐ Encephalitis ☐<br>Meningitis ☐ Seizures Febrile ☐<br>Seizures Afebrile ☐ Sepsis ☐ | | | |
| Other Adverse Events Requiring investigation<br>Yes ☐ No ☐ | | | Anaphylaxis ☐ Persistent screaming ☐<br>Osteitis/Osteomyelitis ☐<br>Hypotonic Hyporesponsive Episode ☐<br>Toxic Shock Syndrome ☐ | | | |
| Adverse Events Not Requiring investigation<br>Yes ☐ No ☐ | | | Allergic reaction ☐ Arthralgia ☐<br>High fever (>39°C / 102°F) ☐<br>Nodule at the injection site ☐ | | | |
| **Other Adverse Events:** | | | | | | |
| **Treatment given :** | | | | | | |
| **If referred, date & time for referring to higher centre:** | | | | | | **NA ☐** |

| **Medical History/other** | **Outcome:** |
|---|---|
| | Hospitalized: Yes ☐ No ☐<br>if 'Yes', Hospital Registration No: ----------<br>Still in the hospital ☐<br>Discharged ☐ |
| | Recovered completely ☐, Partially recovered ☐<br>Death ☐ |
| **Reporting source:** | |
| Date of the notification:<br><br><br><br>Name & Signature of the notifying officer:<br><br>Mobile No: | Name of Health Centres: |

## 1.2 Annexure II: AEFI Investigation Form

**A PATIENT INFORMATION**

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

A.2. Address:

A.3. Date of birth: Gender: Male/Female:

A.4. Mobile no (patient or guardian):

**B PAST Illness:** Yes ☐ No ☐ Unknown ☐; if yes describe:

**B1. PRESENT ILLNESS/OUTCOME**

| | | |
|---|---|---|
| B1. What is the AEFI reported?<br>_____<br>B2. Date and time of onset<br>_____<br>B3. Where was the patient treated, name and type of Health Facility (HF)?<br>Name of HF:<br>Type of HF (PHC/hospital etc.): | B4. Was the patient admitted to hospital?<br>Yes ☐ No ☐ Unknown ☐<br>B5. If yes, date of admission:<br>_____<br>_____ | B7. Outcome of the case:<br>Recovered ☐ Discharged and partially recovered ☐<br>Still hospitalized ☐ Died ☐<br>Unknown ☐<br>B8. Date of discharge, Referral or death:<br>_____<br>B9. If referred, name of hospital referred to<br>_____ |

**C. CLINICAL DATA**

(Case definition: any untoward medical occurrence following immunization which does not necessarily have a causal relationship with the usage of the vaccine)

| C1. Symptoms and signs if present. | C2. Date of onset (Write No if not present) | C3. Relevant findings from laboratory investigations | C4. Treatment given or remarks |
|---|---|---|---|
| Fever | | | |
| Inconsolable cry | | | |
| Painful swelling at the injection site | | | |
| Enlarged tender axillary lymph nodes | | | |
| Convulsions | | | |
| Altered sensorium | | | |
| Any other symptoms and signs: | | | |

| **D. PAST MEDICAL AND FAMILY HISTORY** | | | | | |
|---|---|---|---|---|---|
| | | Yes | No | Unknown | if yes (specify) |
| D1. | Existing congenital disease | ☐ | ☐ | ☐ | |
| D2. | Persisting underlying disease | ☐ | ☐ | ☐ | |
| D3. | Previous history of significant illness | ☐ | ☐ | ☐ | |
| D4. | Family history of similar event | ☐ | ☐ | ☐ | |
| D5. | Previous history of similar event | ☐ | ☐ | ☐ | |

| **E. OTHER RELEVANT HISTORY** | | | | |
|---|---|---|---|---|
| | | Yes | No | Specify |
| E1. | Delays in taking patient to the hospital | ☐ | ☐ | |
| E2. | Delays in transferring patient to the hospital for specialized hospital | ☐ | ☐ | |
| E3. | Delays in receiving treatment | ☐ | ☐ | |

| **F. IMMUNIZATION HISTORY** | | |
|---|---|---|
| F1. | Delays in taking patient to the hospital | Date and Time of immunization of interest: |

| F2. | Delays in transferring patient to the hospital for specialized hospital | Site of immunization: Hospital ☐ PHC ☐ ORC ☐ School ☐ Others.....: | | | |
|---|---|---|---|---|---|
| F3. Type of vaccine (please √ appropriate box) | F4. Dose | F5. Expiry Date | F6. Batch No. | F7. Manufacturer | F8. Diluents Batch No. & Expiry date |
| ☐ Hep B<br>☐ BCG | | | | | |
| ☐ OPV<br>☐ Penta<br>☐ PCV | | | | | |
| ☐ MR<br>☐ DPT | | | | | |
| ☐ IPV | | | | | |
| ☐ HPV | | | | | |
| ☐ Td | | | | | |
| ☐ Influenza | | | | | |
| ☐ COVID-19 | | | | | |

| **G. INFORMATION ON COLD CHAIN/STORAGE/VACCINATION TECHNIQUE** | | | |
|---|---|---|---|
| G1. Vaccines and diluents stored in the<br>☐ Refrigerator<br>☐ Others<br><br>Specify_____ | G2. Vaccine transported in a<br>☐ Vaccine carrier<br>☐ Cold box<br>☐ Others<br><br>Specify_____ | G3. Status of the data lodger for 1 month period prior to the date of the immunization:<br><br>Max. temperature:_____<br><br>Min. temperature:_____ | G4.1. VVM stage_____☐<br><br>G4.2. Temperature at the main compartment of the refrigerator _____☐ |

| At the time of the observation of the immunization | Satisfactory | Unsatisfactory | Not observed |
|---|---|---|---|
| G5. Maintenance of cold chain<br>1. Packing of vaccine<br>2. Maintenance of cold chain in unopened/opened vials during immunization | ☐<br>☐ | ☐<br>☐ | ☐<br>☐ |

| | | | |
|---|---|---|---|
| G6. Vaccination procedure<br>1. Reconstitution<br>2. Drawing of vaccine<br>3. Injection technique | ☐<br>☐<br>☐ | ☐<br>☐<br>☐ | ☐<br>☐<br>☐ |
| G7. Please √ the appropriate box. The syringe used was:<br>Reusable Disposable AD syringes | | | |

| H. | **AEFI IN THE CLINIC CENTRE / FIELD** | | | |
|---|---|---|---|---|
| **H1.** | Any history of similar events reported among those vaccinated: | **Yes** | **No** | **Unknown** |
| **H2.** | At the same clinic session | ☐ | ☐ | ☐ |
| **H3** | Using same vaccine at previous clinic session at the same clinic centre | ☐ | ☐ | ☐ |
| **H4.** | Using same vaccine at the other clinic centre | ☐ | ☐ | ☐ |
| **H5.** | History of similar events reported among those unimmunized | ☐ | ☐ | ☐ |

| **I. ONCLUSION 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 or add remarks on the cause in below given area** | | | | | |
| | | | | | |

**Others information:** Others information: Others information:

Place of delivery:

Nos. of children immunized on the same day with the same vaccine, if different batches of vaccines used please specify number for each batch:

1.

2.

3.

if different batches of vaccines used please specify number for each batch:

Corrective action taken by the investigators .....

Remarks.....

Signature.....

Name.....

Designation.....

Date.....

*** THE END ***

## 1.3 Annexure III: Investigation of Death Following Immunization

| |
|---|
| 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 the 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:<br>• Neonatal or infant death in family:<br>• Details of siblings:<br>• Medical history of siblings: | | | |
| 10) Details of management of the case at the hospital | | | |
| • Name of the hospital:<br>• Date and time of admission:<br>• Name of doctor taking care of the patient: | | | |
| **Clinical description and clinical findings as per admitting doctor** .....<br>.....<br>..... | | | |
| **Details of subsequent management as per records**<br>.....<br>..... | | | |

| **Investigations** | | |
|---|---|---|
| | **Investigation** | **Interpretation** |
| Haematological | | |
| Biochemistry | | |
| Radiological | | |
| Others | | |

| **Management** |
|---|
| • Pharmacological: |
| • Non-pharmacological: |
| • Probable diagnosis: |

## 1.4 Annexure IV: Laboratory Request Form (LRF)

<table>
<tr><td colspan="6">AEFI – LABORATORY REQUEST FORM (LRF)<br>(To be accompanied with specimens)</td></tr>
<tr><td colspan="6">(For Serious Adverse Events Following Immunization)</td></tr>
<tr><td colspan="6">AEFI category (circle): Death / Hospitalized / Cluster / Disability</td></tr>
<tr><td colspan="6">Health information:</td></tr>
<tr><td colspan="3">District:</td><td colspan="3">Case ID:</td></tr>
<tr><td colspan="3">Health centre:</td><td colspan="3">Date of filling LRF (dd/mm/yyyy): ___/____/_____</td></tr>
<tr><td colspan="3">Name &designation of the person sending the specimen:</td><td colspan="3">Phone Number:</td></tr>
<tr><td colspan="6">Case information:</td></tr>
<tr><td colspan="3">Case Name:</td><td colspan="3">Date of Birth (dd/mm/yyyy): ____/____/_____</td></tr>
<tr><td colspan="3">Age: _____ yrs_____ months</td><td colspan="3">Sex:</td></tr>
<tr><td colspan="3">Residential address:</td><td colspan="3">Phone number:</td></tr>
<tr><td colspan="3">Date of vaccination:</td><td colspan="3">Date of onset:</td></tr>
<tr><td colspan="3">Date of collection of specimens:</td><td colspan="3">Time of collection of specimens:</td></tr>
<tr><td colspan="6">Description of samples:</td></tr>
<tr><td colspan="6">For vaccines/diluents (to be transported in reverse cold chain)/syringes/AD/reconstitution:</td></tr>
<tr><td>Mention vaccine/diluent</td><td>Quantity Sent</td><td>Name of Manufacturer</td><td>Batch No.</td><td>Manufacturing Date</td><td>Expiry Date</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="6">For biological specimens</td></tr>
<tr><td colspan="6">Type of specimen:</td></tr>
<tr><td colspan="6">Test requested:</td></tr>
<tr><td colspan="6">Preliminary clinical diagnosis (working hypothesis):</td></tr>
<tr><td colspan="6">To be completed by RCDC:</td></tr>
<tr><td colspan="3">Date of receipt of specimen at laboratory</td><td colspan="3">Name of person receiving specimen(s) at laboratory</td></tr>
</table>

| | |
|---|---|
| Condition of specimen upon receipt at lab (circle):<br>Good/ Poor/ Unknown | Comments: |
| Date result sent from RCDC | Name and signature of the official: |

## 1.5 Annexure V: Worksheet used for the Causality Assessment

### Step 1 (Eligibility)

| *Patient ID/Name :* | *DoB/Age:* | *Sex: Male/Female* |
|---|---|---|
| Name one of the vaccines administered before this event | What is the Valid Diagnosis? | Does the diagnosis meet a case definition? |
| | | |

**Create your question on causality here**

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

Is this case eligible for causality assessment? Yes/No; If, "Yes", proceed to step 2

### Step 2 (Event Checklist) ✓ (check) all boxes that apply

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

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

## Interpretation of the questions in Annexure V

**I. Is there strong evidence for other causes?**

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

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

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

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

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

### Vaccine Product(s)

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

- Refers to the vaccine information sheet of WHO and the package insert of the vaccines to find a list of common vaccine reactions that are known to be associated with that vaccine and their expected frequency. These documents are available in the AEFI reference tool kit and also at https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/guidance/reaction-rates-information-sheets.

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

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

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

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

### Vaccine Quality

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

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

**Immunization Error**

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

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

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

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

- Poor vaccination technique e.g. touching the hypodermic needle while injecting can cause abscess. Administration of the contaminated vaccine may lead to either local (cellulitis or abscess) or systemic (sepsis or toxic shock syndrome) adverse reaction. Abscess is the most common program error which is reported.

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

- Abnormal colour, turbidity or presence of visible contaminants may be the first indication that the vaccine contents are abnormal or unsterile and may have caused an AEFI such as injection site abscess. It is important to talk to the vaccinator and ask whether any abnormality in

the vaccine vial or diluent contents was noticed and also examine the remaining contents of the same vial and other vials of the same batch in the PHC cold chain room.

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

- AEFIs including deaths have resulted because of accidental use of the wrong product or the wrong diluent. This may occur because of improper storage and/or improper selection. Vaccine failure can result if the entire content is not dissolved when freeze-dried vaccines are used or if the cold chain is not maintained properly.

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

- Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluent where applicable) may result in:
  - » vaccine failure as a result of inactivation of the active vaccine components
  - » systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines.
- Reconstituted vaccines used beyond the prescribed time and recommended maintenance conditions can result in vaccine failure and/or disease in the recipient (e.g. toxic shock syndrome). Usually, this happens when a:
  - » reconstituted vaccines are used beyond the recommended time (>4 hours)
  - » reconstituted vaccines are not kept under proper cold chain at the session site

- » reconstituted vaccines are used in more than one session sites
- » syringe used for reconstituting a vaccine vial is reused for reconstituting other vaccine vials

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

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

- neurological, muscular, vascular or bone injury from the use of an incorrect injection site, equipment or technique
- systemic and/or local reactions following administration of an incorrect dose
- sterile abscess following subcutaneous instead of intramuscular injection of alum adjuvanted vaccines – usually a result of using a needle that is too short to reach the muscle layer.
- administration of injectable vaccines orally or oral vaccines as injections.
- Immunization Anxiety (Immunization Triggered Stress Response - ITSR)
- Immunization anxiety reactions can occur singly or in clusters. Adolescents, especially if immunized in mass clinical settings, are more prone to have anxiety-related vasovagal reactions resulting in fainting, sometimes accompanied by tonic-clonic seizure-like movements (pseudo- seizure).

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

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

**II (time). II.I In this patient, did the event occur within a plausible time window after vaccine administration?**

- It is important to confirm if the event took place within a "plausible" time window of increased risk.

**III.a Is there a body of published evidence (systematic reviews, Global Advisory Committee on Vaccine Safety-GACVS reviews42, Cochrane reviews etc.) against a causal association between the vaccine and the event?**

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

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

- The occurrence of an AEFI after a previous dose of a similar vaccine should be handled cautiously.

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

- It is important to verify if a similar event occurred in the vaccinee and family in the past independent of immunization.

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

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

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

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

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

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

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

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