ETHIOPIAN FOOD AND DRUG AUTHORITY

PHARMACOVIGILANCE AND CLINICAL TRIAL LEAD EXECUTIVE OFFICE

National Guideline for Monitoring Adverse Events Following Immunization

Document No.:	EFDA/GDL/016	**Version No:**	004
Date of approval:	03 June	**Date of First issue:**	25 June

Document History

Version No.	Reason for Amendment	Effective Date
001	New version	January, 2005
002	Revised to include investigation techniques, specimen collection, managing AEFIs and communicating with the media, bring stakeholders together and allow for networking and improved collaboration in the process of detecting, analysing and preventing AEFIs.	February, 2016
003	Amended to incorporate the roles and responsibilities of some stakeholders in AEFI reporting and investigation, clearly indicates AEFI reporting route and timeline, analysis of AEFI data and also includes Communication and media management	February, 2018

004	Revised to provides complete guidance on the detection and reporting of AEFI, channels of reporting of AEFIs, investigation and causality assessment of AEFI cases. Includes all antigens given in Ethiopia even in routine immunization programs Moreover, it incorporates roles and responsibilities of all AEFI stakeholders at all levels to take active part in the strengthening of the AEFI surveillance system in Ethiopia and vaccine safety and risk communication strategy	June, 2024

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Foreword

Vaccines are principally used to protect individuals predominantly children from acquiring deadly infectious diseases which are vaccine preventable. Modern vaccines are generally safe and effective. However, they may cause Adverse Events Following Immunization (AEFI). An AEFI may be caused by a vaccine reaction, or it may be caused by an error in administration or handling of the vaccine. It may also be due to anxiety related reaction or coincidental event. Most of the AEFIs are mild or moderate but sometimes serious AEFIs may happen. As vaccines are usually given to healthy individuals, there is low public tolerance to AEFIs. AEFIs may lead to public suspicions of vaccines and parents may refuse further immunization for their children. Hence, monitoring AEFI is of paramount importance in a healthcare system of any country as this helps sustain public confidence in the immunization program.

AEFI surveillance system utilizes different tools such as guidelines, AEFI recording and reporting tools, and procedures geared to assure public health protection using vaccines with proven safety profile. In Ethiopia, the current system for monitoring medicine safety (pharmacovigilance) is coordinated by the Ethiopian Food Drug Authority (EFDA), the National Regulatory Authority (NRA) mandated by proclamation 1112/2019 to ensure the safety, quality and efficacy medicines and other medical technologies.

EFDA has been working to improve patient care and safety in relation to the use of medicines and other medical interventions in collaboration with various stakeholders. It is essential that all stakeholders including the Expanded Programme on Immunization (EPI), Ethiopian Public Health Institute (EPHI), vaccine manufacturers, laboratories, healthcare providers and development partners make rigorous efforts to provide documented evidence on vaccine safety through an effective AEFI surveillance system. This will ensure the provision of best immunization services to the community including effective monitoring and response to AEFIs.

It is envisaged that this guideline provides complete guidance on the detection and reporting of AEFIs; channels of reporting of AEFIs; investigation and causality assessment of AEFI cases. Moreover, it guides all AEFI stakeholders at all levels to take active part in the strengthening of the AEFI surveillance system in Ethiopia.

It is with great pleasure to present this revised (4^{th} edition) Guideline for Monitoring of AEFI in Ethiopia. I hope all stakeholders will use this guideline effectively as a guide towards maintaining vaccine safety and ultimately improve immunization programme.

Finally, I would like to take this opportunity to thank all individuals, institutions/organizations and partners involved in the revision, printing and distribution of this guideline. I would also like to

call upon all interested bodies/individuals to continue their usual support through forwarding their comments and suggestions for improvements to the Ethiopian Food and Drug Authority through P.O. Box 5681 Addis Ababa, Ethiopia, Tel.251-115524122, e-mail contactefda@efda.gov.et.

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Acknowledgements

EFDA would like to acknowledge the World Health Organization (WHO), the Ohio State University Global One Health Initiative (GOHi), and the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) for their financial and technical support during the revision of this guideline. The Authority would also like to extend its gratitude to all participants of the validation workshop for their valuable comments and contributions. Finally, EFDA extends its heartfelt appreciation and gratitude to the experts listed below for their professional and scientific contributions in the development and revision of this guideline.

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Glossary

AEFI	Any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally associated events are also temporally associated (i.e. they occur after vaccine administration), but events which are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of AEFI surveillance, it is a systematic review of data about AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health. facility, and/or a vial of vaccine or a batch of vaccines.
Coincidental events	An AEFI caused by something other than the vaccine product, immunization error or immunization anxiety.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/ severe febrile illness.
Crisis communication	Is an adjusted response to an incident, which aims to restore public confidence by informing the public on what went wrong, why, and what is being done in response.
Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human "body" (self) and to eliminate "foreign" (non-self) material. This discriminatory ability provides protection

	from infectious diseases since most microbes are identified as foreign by the immune system.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Immunization error-related reaction	An AEFI caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse events surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g., transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Monitoring	Monitoring is a continuous assessment that aims at providing all stakeholders with early detailed information on the progress or delay of the on-going assessed activities.
Non-serious AEFI	An event that is not ‘serious’ and does not pose a potential risk to the health of the recipient. Non-serious AEFIs also should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization or have an impact on the acceptability of immunization in general.
Risk Communication	Is enable people at risk to take informed decisions to protect themselves and their loved ones.
Safe injection practice	Practices which ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.

Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe/Severity	The term severe is not synonymous with serious in this context. Severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction).
Signal (safety signal)	Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of an own association, between an intervention and an adverse event or set of related adverse events, which is judged to be of sufficient likelihood to justify verificatory action.
Surveillance	The continuing, systematic collection of data that will be analysed and disseminated to enable decision-making and action to protect the health of populations.
Vaccine	A biological preparation that improves immunity to a particular disease. In addition to the antigen, it contains multiple components (excipients), and each component may have unique safety implications.
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process, which maintains the highest efficacy of and lowest adverse reaction to a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

Abbreviation and/or Acronyms

ADR	adverse drug reaction
AEFI	adverse events following immunization
ANC	antenatal care
BCG	Bacillus Calmette Guerin vaccine ~~for tuberculosis~~
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Corona Virus Disease 2019
DT	Diphtheria and Tetanus vaccine
DTaP	Diphtheria, Tetanus and acellular Pertussis ~~vaccine~~
DTPa-HepB-Hib	Diphtheria, Tetanus, acellular Pertussis, Hepatitis B and Haemophilus influenza vaccine
DTwP	Diphtheria, Tetanus, and whole cell Pertussis ~~vaccine~~
EFDA	Ethiopian Food and Drug Authority
EPHI	Ethiopian Public Health Institute
EPI	Expanded Program on Immunization
EPSS	Ethiopian Pharmaceuticals Supply Service
GACVS	Global Advisory Committee on Vaccine Safety
GVAP	Global Vaccine Action Plan
Hep B	Hepatitis B ~~vaccine~~
Hib	haemophilus influenza type b ~~vaccine~~
ICSR	Individual Case Safety Report
IPV	Inactivated Polio Vaccine
LAV	Live Attenuated Vaccine
MAH	Marketing Authorization Holder
MMR	Measles, Mumps and Rubella ~~vaccine~~
MOH	Ministry of Health

NRA	National Regulatory Authority
OPD	Outpatient Department
OPV	Oral Polio Vaccine

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1. Introduction

1.1. Background

The immunization program is one of the most cost-effective health interventions, with proven strategies to reach the most hard-to-reach and vulnerable populations. The overall goal of the immunization program is to protect the health and wellbeing of the entire population, including infants, children, adolescent girls, and pregnant women, from vaccine-preventable diseases. The World Health Assembly's Immunization Agenda 2030 envisions a world where everyone, everywhere, at every age, fully benefits from vaccines to improve health and well-being.

In Ethiopia, the immunization program has achieved a remarkable reduction in morbidity and mortality from vaccine-preventable diseases. The antigens in the routine immunization program protect against diphtheria, pertussis, haemophilus influenzae type B, hepatitis B, tetanus, polio, tuberculosis, pneumococcus, rotavirus, measles, human papillomavirus, and COVID-19. Newly introduced vaccines also target diseases such as hepatitis B, cholera, malaria, meningococcal meningitis A, and yellow fever.

Vaccines are biological substances administered to elicit immunity against specific diseases. These products are formulated with adjuvants and/or excipients and, like all medical products, may cause adverse events following their administration. There is no such thing as a "perfect" vaccine that protects everyone and is entirely safe for all. Like other medicinal products, vaccines are not free from adverse events.

An AEFI is any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the vaccine. If not rapidly and effectively addressed, AEFI can undermine confidence in a vaccine and ultimately impact immunization coverage and disease incidence. AEFIs can arise due to a variety of reasons, including events inherent to the vaccine product, issues related to quality, immunization error, immunization anxiety, or coincidental occurrences.

The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety has indicated the AEFI surveillance system as a key component of global AEFI reporting and part of the Global Vaccine Action Plan Monitoring and Evaluation framework. This system serves as a benchmark for evaluating vaccine safety performance at national, regional, and global levels and monitoring progress in AEFI surveillance across all age groups. Although AEFIs are mostly mild and rarely serious, measures need to be implemented to monitor and prevent their occurrence and to take appropriate regulatory actions if necessary.

EFDA is mandated by Proclamation No. 1112/2019 to regulate and protect public health by ensuring the safety, efficacy, and quality of vaccines. EFDA has established pharmacovigilance and post-marketing surveillance systems to assure vaccine safety. It sets out procedures for reporting, analysing, and providing feedback on vaccine safety data from all key stakeholders in the vaccine supply chain. Reporting AEFIs and subsequent investigation may lead to regulatory actions, including withdrawing the marketing authorization of a vaccine, instructing manufacturers to change product labels, restricting the use of vaccines to specific groups, or recalling defective vaccine batches from the market. Thus, a robust AEFI monitoring system is essential for detecting, managing, and preventing AEFIs.

Purpose

This guideline describes the process of AEFI detection, notification, reporting, investigation, data management, causality assessment and feedback provision. In addition, it describes the roles and responsibilities of all stakeholders, provides tools and procedures needed to report and manage AEFIs and guides vaccine safety and risk communication strategies in the implementation of vaccine pharmacovigilance system. It also serves as a reference material for healthcare providers, regulators, expanded program on immunization (EPI) and other program managers.

1.2. Scope

This guideline applies to monitor AEFI surveillance activities from National Immunization Program (NIP), and it applies to all stakeholders involved in AEFI monitoring system at all levels.

1.3. Objective

The objective of this guideline is to:

- Provide guidance on detection, management, reporting, investigation, data management, casualty assessment, prevention and feedback provision on AEFI.
- Identify stakeholders involved in AEFI monitoring system and define their roles and responsibilities.
- Provide guidance on the different tools used in the AEFI monitoring system.
- Provide guidance on effective vaccine safety and risk communication.

2. Basic Concepts of Vaccines and Adverse Events Following Immunization

2.1. Vaccines

A vaccine is a biological product that produces and enhances immunity to the particular vaccine-preventable diseases (VPDs) for which it is targeted. A vaccine contains the disease-causing microorganism or virus, or a portion of it, in a form that is incapable of causing the actual disease. It is usually made from either live attenuated or inactivated (killed) forms of the microbe or from its toxin or one of its surface proteins. A vaccine can also be made from a messenger RNA (mRNA) coding for an antigenic protein that is generated in vitro and encased with suitable material to ensure delivery into the cell.

Vaccines may be monovalent or multivalent (polyvalent). A monovalent vaccine contains a single strain of a single antigen or immunogen (e.g., measles vaccine), whereas a polyvalent vaccine contains two or more strains or serotypes of the same antigen or immunogen (e.g., bivalent oral polio vaccine [bOPV] and inactivated polio vaccine [IPV], each of which contains two live and three attenuated poliovirus types, respectively).

Combination vaccines contain two or more different antigens (e.g., Td, DTPa-HepB-Hib). The potential advantages of combination vaccines include reducing the cost and difficulty of shipping, storing, and administering multiple vaccines, avoiding multiple injections, reducing the cost of extra health-care visits, improving the timeliness of vaccination, and facilitating the addition of new vaccines into immunization programs. Combining antigens usually does not increase the risk of adverse reactions and can lead to an overall reduction in adverse reactions. For instance, it can decrease the number of anxiety-related reactions and the chances of immunization error-related reactions.

2.1.1. Classification of vaccines

There are different types of vaccines, such as live attenuated, inactivated (killed antigen), subunit (purified antigen), toxoids (inactivated toxic compounds), viral vector-based vaccines, and nucleic acid vaccines (messenger RNA and DNA vaccines). The characteristics of these vaccines differ, and these characteristics determine how the vaccine works.

Live Attenuated Vaccine (LAV): Live attenuated vaccines (LAVs) are derived from “wild,” or disease-causing, viruses or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. The resulting vaccine organism retains the ability to replicate (grow) in the vaccinated person and produce immunity but usually does not cause illness.

The immune response to a LAV is virtually identical to that produced by a natural infection. For LAVs, the first dose usually provides protection, and an additional dose is given to ensure seroconversion. Immunity following live vaccines is long-lasting, and booster doses are generally not necessary, except for the oral polio vaccine, which requires multiple doses.

LAVs are labile and can be damaged or destroyed by heat and light, so they must be handled and stored carefully. One inherent problem of live attenuated vaccines is the potential for reversion to the virulent strain; however, this risk is considerably minimized because multiple mutations are usually introduced.

Globally, available LAVs include vaccines for measles, mumps, rubella, varicella, yellow fever, oral polio, and influenza (intranasal). Live attenuated bacterial vaccines include BCG and oral typhoid vaccines.

Inactivated whole-cell vaccines are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formalin). Because they are not alive, they cannot grow in a vaccinated individual. Inactivated vaccines are generally safer than LAV, with no risk of inducing the disease. Unlike live antigens, inactivated antigens are usually not affected by circulating antibodies. They are often more stable than LAVs. Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only "primes" the immune system. A protective immune response is developed after multiple subsequent doses. In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral and little or no cellular immunity results.

Some of the safety issues that may need to be considered for inactivated vaccines include incomplete inactivation of viral particles causing the vaccine to retain virulence and cause disease, and development of vaccine-associated enhanced disease (VAED) when vaccinated individuals encounter the pathogen after being vaccinated. Some of the currently available inactivated vaccines include inactivated poliovirus vaccine (IPV), hepatitis A, anti-Rabies and etc.

Subunit vaccines: sometimes called acellular vaccines contain purified proteins/sugar of disease-causing organism that stimulates immune cells. Subunit vaccines are considered very safe because these purified proteins are incapable of causing disease. The types of subunit vaccines are described in Table 1.

Table 1: Types of subunit vaccines.

Type	Description	Examples
Protein-based vaccines	Contain specific isolated proteins from viral or bacterial pathogens	Hepatitis B vaccine, acellular pertussis vaccine, human papillomavirus vaccine
Polysaccharide-based vaccine	Contain chains of sugar-molecules (polysaccharides) found in the cell walls of some bacteria	Meningococcal polysaccharide vaccine, pneumococcal polysaccharide vaccine
Conjugated vaccines	Contain combination of a weak antigen with a strong antigen as a carrier	Pneumococcal conjugate vaccines, haemophilus influenzae type b conjugate vaccine, meningitis A and B conjugate vaccines

Toxoid Vaccines: use a toxin (harmful product) made by the germ that causes a disease. They are produced by purifying the toxin and altering it chemically usually with formaldehyde (e.g. tetanus diphtheria (Td). While no longer toxic, the toxoid is still capable of inducing a specific immune response protective against the effects of the toxin. That means the immune response is targeted to the toxin instead of the whole germ. In some bacterial infections (e.g. diphtheria, tetanus), the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete.

Viral vector-based vaccines: These vaccines are developed by introducing the genetic sequence coding for the antigen from the pathogen into a viral vector that has been previously rendered non-virulent by genetic techniques. Some viral-vector-based vaccines can replicate in the host cell (replicating viral-vector vaccines), such as the recently approved Ebola vaccine and some vectors do not replicate in the host cells (non-replicating viral vector vaccines) such as Janssen and AstraZeneca Covid-19 vaccines, depending on modifications introduced into the vector genome.

Nucleic acid vaccines: use genetic material from a disease-causing virus or bacterium (a pathogen) to stimulate an immune response against it. Depending on the vaccine, the genetic material could be DNA or RNA; in both cases, it provides the instructions for making a specific protein from the pathogen (gives your body instructions to make specific foreign proteins), which the immune system will recognize as foreign (an antigen). Once, inserted into host cells, this

genetic material is read by the cell's protein-making machinery and used to manufacture antigens, which then trigger an immune response.

Messenger ribonucleic acid (mRNA) Vaccines: These vaccines are based on mRNA coding for an antigenic protein that is generated in vitro and encased with suitable material (e.g., lipid-based nanoparticle emulsion) that assures the delivery into the cell. The mRNA vaccines have several benefits compared to other types of vaccines, including shorter manufacturing times and because they do not contain a live virus, no risk of causing disease in the person getting vaccinated. These vaccines have been shown to stimulate innate immunity. Therefore immune-mediated adverse events are also possible with this type of vaccine. Residual molecules, originating from raw materials, could induce unexpected immune responses.

Deoxyribonucleic acid (DNA) vaccines: use a gene from a virus or bacteria to stimulate the immune system. The nucleic-acid segment is integrated into a bacterial plasmid carrier that contains the encoding segment for the antigen, plus a promoter and other residual segments from the virus or bacteria of origin. The potential for integration into host cell DNA poses a theoretical risk; however, studies to date have shown that no retrovirus elements are available for their reverse transcription into DNA.

2.1.2. Other components of vaccines

In addition to the primary antigen(s), vaccines also contain small quantities of other substances which may cause AEFI. These include:

Adjuvants: a substance that is sometimes added to a vaccine to enhance the immune response by degree and/or duration, making it possible to reduce the amount of immunogenic per dose or the total number of doses needed to achieve immunity. The commonly used adjuvants are aluminium salts (aluminium hydroxide, aluminium phosphate or potassium aluminium sulphate) which primarily enhance the immune response to proteins. They have been shown to be safe over several decades of use. Rarely, they may cause injection site reactions, including subcutaneous nodules, sterile abscesses, granulomatous inflammation or contact hypersensitivity.

Antibiotics: are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. For example, MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose. Recipients who are known to be allergic to neomycin should not be vaccinated with neomycin containing vaccine and be closely observed if vaccinated unknowingly so that any allergic reaction can be treated immediately.

Preservatives: are chemicals (e.g. thiomersal, phenol derivatives) that are added to a killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and remain in the vial to prevent serious secondary infections in multi-dose vials as a result of bacterial or fungal contamination after they are opened.

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

2.1.3. Contraindications and precautions to vaccination

A contraindication to vaccination is a rare characteristic/condition in a recipient that increases the risk of a serious adverse reaction if the vaccine is given. Ignoring contraindications can lead to avoidable vaccine reactions. One of the most serious reactions following vaccination is anaphylaxis which is the only contraindication applicable to subsequent doses of the same vaccine. Most contraindications such as severe acute illnesses (e.g. acute respiratory tract infection) or treatment with steroids are temporary and the vaccination can be administered later. These are called temporary or relative contraindications. Precautions, in contrast, are events or conditions that should be considered in determining if the benefits of the vaccine outweigh the risks (especially if the recipient is immunocompromised or pregnant). Precautions stated in the product labelling may sometimes be inappropriately interpreted as contraindications, resulting in missed opportunities to vaccinate.

2.2. Adverse Events Following Immunization

An AEFI is any untoward medical occurrence (unfavourable or unintended sign, abnormal laboratory finding, symptom, or disease) that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. Reported adverse events can either be true adverse events i.e. resulting from the vaccine or immunization process or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization. The five categories of AEFI as defined by the Council for International Organizations of Medical Sciences (CIOMS) and WHO are described in the Table 2.

Table 2: Cause-specific type of AEFIs.

Cause-specific type of AEFI	Definition

Vaccine product-related reaction	An AEFI 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 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.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

2.2.1. Vaccine Reactions

Vaccine reactions may be grouped into two broad categories: based on cause, and seriousness and frequency.

a. **Cause-specific vaccine reactions.**

Vaccine product-related reaction: this is an individual's reaction to the inherent properties of the vaccine, even when the vaccine has been prepared, handled and administered correctly. Most often the exact mechanism of a vaccine product-related reaction is poorly understood. The reaction may be due to an idiosyncratic immune mediate reaction (e.g. anaphylaxis) or to replication of the vaccine-associated microbial agent (e.g. vaccine-associated poliomyelitis following OPV which contains attenuated live virus).

Vaccine quality defect-related reaction: this is due to a defect in a vaccine (or its administration device) that occurred during the manufacturing process. Such a defect may have an impact on an individual's response and thus increase the risk of adverse vaccine reactions. Insufficient inactivation of wild-type vaccine agents (e.g. wild polio virus) during the manufacturing process or contamination introduced during the manufacturing process could cause vaccine quality defect-related reactions.

b. **Vaccine reactions by seriousness and frequency**

Most vaccine reactions are minor and subside on their own. Serious reactions are very rare and, in general, do not result in death or long-term disability. Table 3 describes the frequency of occurrence of reported adverse events.

Table 3: Frequency of occurrence of reported adverse reactions.

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

Common or minor vaccine reactions are caused when the recipient's immune system reacts to antigens or the vaccine's components (e.g. aluminium adjuvant, stabilizers or preservatives) contained in the vaccine. Minor AEFIs could be local or systemic. Local reactions include pain, swelling and redness at the injection site while systemic reactions include fever, irritability, malaise, and etc. Some examples of the common and very common vaccine reactions are presented in Table 4.

Table 4: Common and very common minor vaccine reactions by antigen type.

Vaccine	**Local adverse events**	**Fever (> 38^0C)**	**Systemic symptoms**
BCG	Injection site papule and mild ulceration (in almost all vaccinees)	-	-
Hepatitis B	Injection site pain (3-29%) Injection site pain (3%) Erythema (3%)	1 – 6%	Headache (3%)
Hib	Injection site reaction (10%)	2-10%	Irritability (35-71%
Measles	Injection site reaction (17-30%)	5-15%	Rash (2-5%)
OPV	-	11.7%	Abdominal pain (17.2%)

			Headache (22.4%) Diarrhoea (9.9%) Asthenia (7,5%) GI* (33.5%) Nervous system (29.3%)
DPT	Local redness (37.4%) Swelling (40.7%) Injection site pain (50.9%)	31.5%	Drowsiness (31.5%) Anorexia (20.9%) Vomiting (6.2%) Fretfulness (53.4%)
Td	Local reaction (38%) Injection site pain (20%	~ 10%	Malaise (3-10%) Headache (3-10%) Fever (3-10%)
HPV	Injection site pain (83%) Swelling (25%)	13%	Urticaria (3%) Headache (26%) Myalgia (2%) Arthralgia (1%) Gastrointestinal disorders (17%)
PCV13	Injection site swelling (25%) Injection site tenderness (25%) Injection site swelling (25%)	33.3%	Drowsiness (50%)
Covid-19 vaccine (Pfizer BioNTech)	Injection site pain (80-89%) Injection site swelling (80-89%) Injection site redness (80-89%)	10-16%	Irritability (70-83%) Malaise (70-83%)
Rotarix	-	1.9 per 1000	-
Rabies (Human Diploid Cell) Vaccine	Injection site pain (60-89.5%) Injection site swelling (60-89.5%) Injection site induration (60-89.5%)		Fever (7-55.6%) Headache (7-55.6%) Dizziness (7-55.6%) GI* (7-55.6%)

Meningitis A	Injection site pain (0.36%) Injection site swelling (0.05%) Injection site abscess (0.03%)	1.87%	Headache (0.66%) Myalgia (0.15%) Asthenia (0.06%) General pruritus (0.26%)
Yellow fever vaccine	Injection site pain/tenderness (14%) Injection site erythema (1.3%) Injection site haematoma (1.9%) Injection site induration (1.4%) Injection site swelling (1.0%)	8.3%	Nausea (5.5%) Vomiting (1.4%) Myalgia (12.8%) Arthralgia (7.5%) Headache (18%) Asthenia (16.6%)
Oral Cholera vaccine	-	-	Headache (10%) Abdominal pain (10%) Tiredness (10%) Vomiting (10%) Loss of appetite (10%)
Hepatitis B birth dose	Injection site pain- (3-29%) Erythema (3%) Injection site swelling (3%)	1-6%	Headache (3%)

*Gastrointestinal symptoms other than mentioned in the table.

Rare or serious vaccine reactions are caused by the body's reaction to a particular component in a vaccine. AEFIs are considered serious by definition if they:

- result in death
- are life-threatening.
- require in-patient hospitalization or prolongation of existing hospitalization.
- result in persistent or significant disability/incapacity
- result in a congenital anomaly/birth defect
- other medically important conditions

The rate of occurrence of some of the rare and more serious reactions has been summarized in the Table 5 on the next page

Table 5: Serious vaccine reactions, onset interval and frequency.

Vaccine	**Reaction**	**Onset Interval**	**Rate per million (1,000,000) doses**
BCG	Suppurative lymphadenitis	2-6 months	100-1000
	BCG osteitis	1-12 months	1 -700
	Disseminated BCG infection	1-12 months	~ 1-2
Hepatitis B	Anaphylaxis	0 – 1 hour	1 – 2
Measles/MMR/MR	Febrile seizures	6-12 days	330
	Thrombocytopenia	15-35 days	30
	Anaphylaxis	0-1 hour	~1
	Encephalopathy	6-12 days	< 1
Oral poliomyelitis	Vaccine associated paralytic poliomyelitis (VAPP)	4-30 days	0.4 – 3
Tetanus Toxoid, DT	Brachial neuritis	2-28 days	5-10
	Anaphylaxis	0-1 hour	1 – 6
Pertussis (DTwP)	Persistent (>3 hours) inconsolable screaming	0-24 hours	1000-6000
	Seizures	0-3 days	80-570
	Hypotonic, hypo-responsive episode (HHE)	0-48 hours	30-990
	Anaphylaxis	0-1 hour	20
	Encephalopathy	0-2 days	0-1
Rotarix	Intussusception	0-21 days	0.1 after first dose
Human Papilloma Virus (HPV) Vaccine	Anaphylaxis	0-2 hours	1.7-2.6
COVID 19-vaccine (AstraZeneca /Covishield)	Thrombosis with thrombocytopenia syndrome (TTS) Guillain-Barre syndrome	Within 4-28 days 21 days after vaccination	
COVID 19-vaccine Janssen and Janssen	Guillain –Barre syndrome Blood clotting disorders	42 days following vaccination.	

Vaccine	Reaction	Onset Interval	Rate per million (1,000,000) doses
	Cerebral venous sinus thrombosis (CVST)	Within 21 days people under the age of 60	

Notes:

- Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose are immune): children over six years unlikely to have febrile seizures.
- VAPP Risk is higher following the first dose (1 in 750,000 compared to 1 in 5.1 million for subsequent doses) and for adults and immune-compromised.
- Seizures are mostly febrile, and the risk depends on age, with much lower risk in infants under the age of 4 months.

2.2.2. Immunization error-related reactions

An adverse event can occur as a result of inappropriate handling, prescribing or administration of a vaccine (Table 6). It is very important to identify and correct these errors as they are preventable (otherwise they may derail the benefits of the immunization program. An immunization error-related reaction may lead to a cluster of events associated with immunization. These clusters are usually associated with a particular provider, health facility, or even a single vial of vaccine that has been inappropriately prepared or contaminated. Immunization error-related reactions can also affect many vials. For example, freezing the vaccine during transport may lead to an increase in local reactions.

Table 6:Immunization error-related reactions.

Immunization error	Examples	Related reaction
Error in vaccine handling	Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the	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

Immunization error	Examples	Related reaction
	vaccine (and its diluents where applicable)	
	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
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 prescription (dose or schedule)	Systemic and/or local reactions, neurological, muscular, vascular or bone 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

2.2.3. Immunization anxiety-related reactions

Individuals and groups can become stressed and may react in anticipation to, and as a result of, any kind of injection. This reaction is unrelated to the constituents of the vaccine product. Fainting (vasovagal syncope or syncope) is relatively common, particularly in children over five years of age and among adolescents. Some children who faint may have a syncopal hypoxic convulsion. Younger children may have breath-holding and vomiting as a common symptom of anxiety. They may also scream or run away to avoid the injection. Some individuals may have needle-phobia.

In group immunization/ mass campaign, mass hysteria is possible, especially if one or more of the vaccine recipients are observed by others to faint or have some other reaction such as itching, weakness of limbs and so on. Hyperventilation as a result of anxiety about the immunization leads

to specific symptoms such as light-headedness, dizziness, and tingling around the mouth and in the hands.

2.2.4. Coincidental events

An event may occur coincidentally with immunization and sometimes be falsely attributed to the vaccine i.e. a chance temporal association is falsely attributed to immunization. Such temporal associations are inevitable, especially during a mass immunization campaign.

Vaccines are normally administered early in life when infections and other illnesses including manifestations of underlying congenital or neurological conditions are common. It is, therefore, possible to encounter many events, including deaths that can be falsely attributed to vaccines through a chance association. For example, the incidence of sudden infant death syndrome (SIDS or "cot death") peaks around the age of early childhood immunization. Consequently, many SIDS cases will occur in children who have recently been immunized. However, several well-designed studies have shown that the association of SIDS and immunization is coincidental and not causal.

Coincidental adverse events may be predictable. The number of events to be expected depends upon the size of the population and the incidence of disease or death in the community. Knowledge of these background rates of disease and deaths, particularly age-specific disease incidence rates, allows estimation of the expected numbers of coincidental events.

3. Prevention and management of AEFI

Vaccines used in the national immunization program are relatively safe and effective. There may be predictable adverse reactions of which most are mild and resolve quickly. However, it is not always possible to predict individuals who might have a mild or serious reaction to a vaccine.

3.1. General principles of prevention and management of AEFI

- Vaccines are very rarely contraindicated. However, it is important to check for contraindications to avoid serious reactions. For example, a vaccine is contraindicated if there is a history of anaphylaxis to a given vaccine or its components in previous vaccinations.
- The proposed waiting time of 15-30 minutes at the health facility will allow the identification and immediate management of medical emergencies like anaphylaxis which manifests most frequently within 5 to 30 minutes of vaccine administration.
- Vaccine anaphylaxis is very rare. However, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all health facilities. All immunization providers need to be trained and develop competence in recognizing and managing anaphylaxis and have epinephrine (adrenaline) available.
- For parents, advice should be given on managing the common minor reactions, in addition to instructions on seeking proper medical care if there are more serious symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions and to adhere to subsequent vaccination schedules as well.
- Antipyretic drugs, in a recommended dosage and schedule, can be given as recommended by the prescriber (or manufacturer). For example, paracetamol, at a dose of up to 15 mg per kg every 6-8 hours with a maximum of four doses in 24 hours, is useful for common minor reactions; it eases pain and reduces fever. However, it is important to advice against overuse of paracetamol or any other antipyretic drug as overdosing may harm the vaccine recipients. A febrile child can be cooled with a tepid sponging or bath, and by wearing light cool clothing. Extra fluids need to be given to children with fever. For a local reaction, a cold cloth applied to the site may ease the pain.
- Using local remedies for any serious vaccine reaction can risk the health and life of the recipients and is strongly discouraged. Early medical care by a qualified clinician will minimize any unwanted outcome and ensure early recovery and may also save lives.

3.2. Prevention and management of immunization error-related reactions

As mentioned in the previous chapter, immunization error-related reactions are preventable, and identification and correction of these errors in a timely manner are important. Prior to the

introduction of auto-disable (AD) syringes, the most common immunization error was an infection as a result of a non-sterile injection and contamination of the vaccine or diluents vial or the injecting device (syringe and/or needle). The infection could manifest as a local reaction (e.g. suppuration, abscess) or a severe systemic reaction (e.g. sepsis, toxic shock syndrome). In addition, there was the perception of a risk linking immunization with blood borne infections. Nevertheless, one needs to consider infection can occur in cases of mass vaccination or in disaster situations, particularly if there is a shortage of supplies or problems with logistics. This can be avoided by proper planning and preparedness of program managers.

The symptoms arising from an immunization error may help to identify the likely cause. For instance, children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) become sick within a few hours with an injection site reaction (local tenderness, redness and swelling) and then develop systemic symptoms (vomiting, diarrhoea, high temperature, rigors and circulatory collapse). Bacteriological examination of the vial, if still available, can confirm the source and type of infection.

Sterile abscesses, while rare (~1 per 100 000 doses) are local reactions from aluminum-containing vaccines, especially DTP. They, along with other local reactions, are more likely to occur if there is inadequate shaking of the vaccine before use, superficial injection and use of a vaccine that had been frozen. Contamination of vaccine or injection equipment can lead to a bacterial abscess. For BCG vaccine, injection abscess can result from improper technique of injection (subcutaneous rather than intradermal injection).

Ignoring contraindications may lead to serious vaccine reactions and is considered an immunization error. The immunization team should be aware of such contraindications and any precautions. Any uncertainty should be referred to a higher level – a program manager, paediatrician or physician. However, it is equally important not to overreact to concerns of false contraindications as this may lead to missed opportunities for vaccination, reducing coverage and thereby increasing the risk of disease in both individuals and the community.

Healthcare providers also need a clear understanding of contraindications and precautions. As mentioned in the previous chapter, precautions are not contraindications, but a decision on whether to vaccinate requires a case-based assessment where the risk of the vaccine is balanced against the potential benefits. The use of live vaccines in pregnancy is a good example of this.

To avoid/minimize immunization error, the following should be observed.

- It is both important and necessary to maintain the cold chain at all levels.
- Vaccines must be reconstituted only with the diluents supplied by the manufacturer.

- Reconstituted vaccine should be maintained in the recommended cold chain and used within six hours after reconstitution; it must be discarded at the end of each immunization session and should never be retained.
- Other than vaccines, no other drugs or substances should be stored in the refrigerator of the immunization centre.
- Immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed.
- Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices.
- Prior to immunization, adequate attention must be given to contraindications.

Follow-up and corrective actions following immunization error-related reactions should be based on the findings of the investigation. Depending on the nature of the immunization error, these actions can be both general (e.g. training and awareness) and specific (e.g. strengthening cold chain maintenance if the problem is found to be related to cold chain issues). Continued monitoring and supportive supervision can help to minimize these adverse events.

3.3. Prevention and management of immunization anxiety-related reactions

Training and awareness to enable health professionals/staff to identify and manage medical emergencies appropriately is important. Fainting does not require any clinical management beyond placing the patient in a recumbent position. Syncopal hypoxic convulsions are short-lived generalized tonic-clonic seizures which can be managed by keeping the child lying down and securing the airway by placing the child on one side to prevent aspiration should the child vomit. The seizure will end spontaneously but, if prolonged or focal, further investigations may be required.

The likelihood of fainting should be anticipated when immunizing older children. It can be reduced by minimizing stress among those awaiting injection, through short waiting times, comfortable room temperatures, preparation of the vaccine outside the recipient's line of vision, and privacy during the procedure.

Sometime, cases with hysteria may even require hospitalization and can cause public concern. Clear explanations about the immunization and a calm, confident delivery will decrease the level of anxiety about the injections and thus reduce the likelihood of an occurrence.

Sometimes a fainting episode can be misdiagnosed as anaphylaxis. Careful observation and clinical judgments are necessary to differentiate. However, an accidental administration of a single dose of adrenaline (intramuscularly) to a vaccine recipient with only syncope does not harm the

vaccine recipient. Besides, it is necessary to promote training and awareness to enable health staff to identify and manage medical emergencies appropriately.

3.4. Management of suspected anaphylaxis or collapse after vaccination

Sudden and severe events occurring post-vaccination, especially syncope, are frequently reported as anaphylaxis. However, anaphylaxis following vaccination is very rare and the risk (in general) is 1.3 episodes per million doses of vaccine administered. The onset of anaphylaxis can occur after several minutes (> 5 minutes) but rarely up to two hours following vaccination. The progression of symptoms is rapid and usually involves multiple body systems, almost always with skin involvement (generalized erythema and/or urticaria) as well as signs of upper and/or lower respiratory tract obstruction and/or circulatory collapse. In young children (though anaphylaxis occurs at any age) limpness, pallor or loss of consciousness may reflect hypotension. In general, the more rapid the onset, the more severe the reaction. For all cases of suspected anaphylaxis, all symptoms and signs must be well documented by health-care providers. Because anaphylaxis is very rare, other causes of sudden and severe symptoms post-immunization that are more common than anaphylaxis need to be considered (Table 7).

Table 7: Conditions that may be mistaken for anaphylaxis post-immunization.

Diagnosis	**Onset: symptoms and signs**
Vasovagal event	Symptoms are usually immediate (< 5 minutes) and commence during the injection process. No skin rash, bradycardia not tachycardia, no respiratory involvement, spontaneous resolution when prone.
Hypotonic hypo-responsive episode	Onset 2-6 hours post-immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, or respiratory or cardiovascular compromise.
Seizure	Onset usually at least 6-8 hours post-vaccination with a killed vaccine. Sudden unresponsiveness usually with tonic-clonic movement, usually febrile, no cardiovascular compromise, no respiratory compromise unless apnoea or aspiration.
Aspiration of oral vaccine (e.g. OPV or Rota virus vaccine)	Immediate respiratory symptoms (cough, gagging, stridor or wheeze) during administration, usually in infants. No skin rash or cardiovascular compromise.

Somatic conversion symptoms	Immediate or delayed respiratory symptoms, syncope, neurological symptoms without objective respiratory or neurological signs.
Severe coincidental diseases	Usually due to coincidental unrecognized congenital heart disease or occult infections. May have respiratory or cardiovascular compromise but there are usually symptoms, signs or investigations to indicate alternate causes.
Immunization- error related	Immediate toxic drug reaction with symptoms and signs due to drug toxicity. Reported with immunization related errors which have resulted from inadvertent administration of a muscle relaxant or insulin.

Emergency equipment must be immediately at hand whenever immunizations are given. Each vaccinator must have an emergency kit with adrenaline (see box on the next page) and be familiar with its dosage and administration (Table 8). The expiry date of the adrenaline should be written on the outside of the emergency kit and the whole kit should be checked three- or four-times a year. Adrenaline that has a brown tinge must be discarded. All vaccinators must be familiar with the practical steps necessary to save lives following anaphylaxis.

Table 8:Adrenaline dosing and administration for treatment of anaphylaxis.

Drug, site, and route of administration	**Frequency of administration**	**Dose**
Adrenaline (epinephrine) 1:1000 Immediate IM injection to the midpoint of the anterolateral aspect of the middle third of the thigh	Repeat every 5-15 minutes as needed until there is a resolution of the anaphylaxis. **Note:** Persisting or worsening cough associated with pulmonary oedema is an important sign of adrenaline overdose and toxicity	Children: 0.01mg/kg Adults: 0.2 mL to a maximum of 0.5 mL If weight is unknown, • Less than 2 years: 0.0625 ml (1/16) • 2-5 years: 0.125 ml (1/8) • 6-11 years: 0.25 ml (1/4)

		• Over 11 years: 0.5 ml (1/2)

Note: Anaphylaxis can also be caused by agents other than vaccines (e.g., drugs).

Contents of an AEFI treatment kit

- Injection adrenaline (1:1000) solution –at least 2 ampoules
- Disposable syringe (insulin type) having mL graduations and IM needle (gauges and length adjusted to targeted recipients) – sets.
- Scalp vein set – 2 sets with medium-bore needles (gauges and length to be adjusted to targeted recipients)
- IV cannula (various sizes, adjusted to targeted recipients)
- Paracetamol (500 mg) – 10 tabs
- IV fluids (Ringer's lactate or normal saline) - 1 unit in plastic bottle
- IV fluid therapy – 1 unit in plastic bottle
- IV drip set – 1 set
- Cotton wool + adhesive tape – 1 each
- AEFI reporting forms.
- Label showing date of inspection, expiry date of injectable adrenaline and shortest expiry date of any of the components.
  - Drug dosage tables for injecting adrenaline
  - At hospital, oxygen support and airway
  - Intubation facility should be available.

4. Adverse Events Following Immunization Surveillance System in Ethiopia

The implementation of AEFI surveillance system is a collaborative action among different stakeholders. AEFI surveillance is an integral part of the national pharmacovigilance activities. It reinforces the safe use of vaccines in the country while helping to maintain public confidence in the immunization program. In Ethiopia, active, spontaneous and stimulated passive surveillance systems are commonly implemented to monitor vaccine safety. AEFI surveillance starts with identification of AEFIs. The identified AEFIs will be notified to the responsible body in the healthcare systems and then be reported to the next level following appropriate channels of reporting. The collected AEFIs will be analysed and for eligible AEFIs, investigation and causality assessment are performed. Finally, based on the findings, corrective action can be taken, and feedback will be communicated to the relevant stakeholders (Fig. 1).

Figure 1: AEFI Surveillance Cycle

4.1. Objectives of AEFI Surveillance System

The major goal of AEFI surveillance is early detection and analysis of adverse events and providing appropriate and quick response in order to decrease the negative impact on the health of individuals and the immunization programme thereby enhancing program credibility and providing country-specific data on vaccine safety. The specific objective of AEFI surveillance is to:

- Quickly detect and respond to any adverse event following vaccination.
- Closely monitor the safety of newly licensed and/or introduced vaccines.
- Detect previously unrecognized reactions of both existing and newly licensed/introduced vaccines.
- Estimate rates of occurrence of AEFIs in the local Ethiopian population compared with clinical trial and international data.
- Detect apparent increases or decreases in the rates of previously reported events.
- Prevent false blame arising from coincidental AEFI, which may have a known or unknown cause unrelated to immunization.

- Identify vaccine lots or brands leading to unusual number and types of vaccine reactions caused by the inherent properties of a vaccine.
- Detect, correct and prevent immunization error-related AEFIs.
- Maintain confidence by properly responding to parent/community/stakeholders' concerns, while increasing awareness (public and professional) about vaccine risk
- Generate new hypotheses about vaccine reactions specific to defined populations in Ethiopia.
- Detect pre-existing conditions that may promote reactions and may represent contraindications or precautions to additional doses.
- Trigger further clinical, epidemiologic, or laboratory investigations regarding a possible causal relationship between a vaccine and the adverse event.
- Share vaccine safety information to the global community to support generation of new and additional information on vaccine safety/signal detection.

4.2. Types of AEFI Surveillance System

There are mainly two types of AEFI surveillance systems: passive and active surveillance. In addition, stimulated passive surveillance can also be used.

Passive surveillance: This encompasses all spontaneous AEFI reporting from immunization service providers/healthcare facilities/clients/patients to the first administrative level in the surveillance system. Passive surveillance systems theoretically allow anyone in a country to report and due to their broad coverage, they can provide the first indication of an unexpected AEFI. Therefore, the main strength of passive surveillance is to detect early the unknown serious AEFI (signals). However, passive surveillance has many limitations, including underreporting. Thus, passive surveillance is often not useful for determining whether the rate of an adverse event has increased. Thus, newly introduced vaccines and/or special immunization campaigns should have added layers of active surveillance and/or epidemiological studies to maximize the effectiveness of passive AEFI surveillance (e.g. enhanced spontaneous surveillance introduced during special immunization campaigns to encourage reporting by service providers or receivers).

Active surveillance: Active (proactive) AEFI surveillance is an active system for the detection of adverse events. This is achieved by active follow-up after vaccination. Events can be detected by asking vaccinees directly or by screening their records. It is best done prospectively. This is primarily used for characterization of the AEFI profile, rates and risk factors, but logistical and resource constraints limit its wide application. Active AEFI surveillance may be carried out only

for selected AEFI or vaccines at selected institutions (sentinel sites). It can also be carried out in the community setting (e.g. cohort event monitoring).

4.3. AEFI Detection and Reporting

All AEFIs brought to the notice of health professionals or detected by them should be reported to the next level using the standard AEFI reporting tools.

4.3.1. Components of AEFI Reporting

4.3.1.1. What to report?

All AEFIs including minor AEFIs, serious AEFIs, events with an unexpected high rate or unusual severity, signals, significant events of unexplained cause after vaccination, events causing significant parental/family/health professional/community concerns, potential immunization errors and adverse events of special interest (AESIs).

4.3.1.2. When to report?

A report must be made as quickly as possible so that an immediate decision can be made on the need for action and investigation. Serious AEFIs, AEFIs as a result of potential immunization errors, clusters of AEFIs, AEFI causing parental or community concern, AEFIs that are known but occur with unexpected frequency and potential signals (unknown/unexpected AEFI) should be reported to EFDA immediately. In case of serious AEFI, vaccine administrators should notify their supervisors and/or woreda immunization officers immediately within 24 hours (over telephone) and send the completed reporting form to EFDA within 48 hours. In case of minor AEFIs, individual case safety reports should be line-listed and sent to the next higher level at least on a monthly basis.

4.3.1.3. Who should report?

All health professionals including nurses, physicians, pharmacists, midwives, public health officers and laboratory technologists.

4.3.1.4. How to report?

Health professionals should report AEFIs using appropriate reporting tools. However, serious adverse evets (SAE) should be reported using standard AEFI reporting yellow form. Commonly utilized AEFI reporting tools include:

Paper-based reporting tools: paper-based (manual) AEFI reporting format (Annex I) can be used to report any suspected individual case safety report (ICSR). The completed ICSR can be delivered

to the responsible body in person, through pre-paid mail (p.o.box 5681) or through emailing of scanned copy to EFDA's email address pharmacovigilance@efda.gov.et.

Electronic reporting tools: health professionals can use electronic reporting tools to report any AEFIs. The electronic reporting tools include Med Safety mobile application and e-reporting system through EFDA's website (www.efda.gov.et).

Toll Free line: The authority has a toll-free call line (**8482)** for notifying/reporting an AEFI by health professionals, vaccine recipients and care givers as well.

It is important that all of the minimum required information is entered into the reporting form, as this is the basis for decisions regarding the need for further investigation. WHO recommended 22 core variables, with 10 identified as critical (minimum information) that should be collected for any AEFI surveillance (Table 9).

Table 9: Core variables: minimum information required for reporting in AEFI surveillance.

Category	**Core variable**	
Identity	Date AEFI report first received at national Centre	*Location (address)
	Country where this AEFI was reported	
Case	*Patient identifier	Sex
	*Date of birth (or) age at time of onset (or) age group at onset	*Medical history
Vaccine	*Primary suspect vaccine name (generic)	*Batch number and expiry date
	Other vaccines given just prior to AEFI.	Vaccine dose number for this particular vaccine
Event	*Date and time of vaccination	*Adverse event
	*Date and time of AEFI onset	*Outcome of AEFI
Reporter	Name of first reporter of AEFI	Email
	Institution/location	Telephone number
	Profession/department	

Other	Comments (if any) by national officer before the report is uploaded to the Global Database

*The ten critical (mandatory) core variables

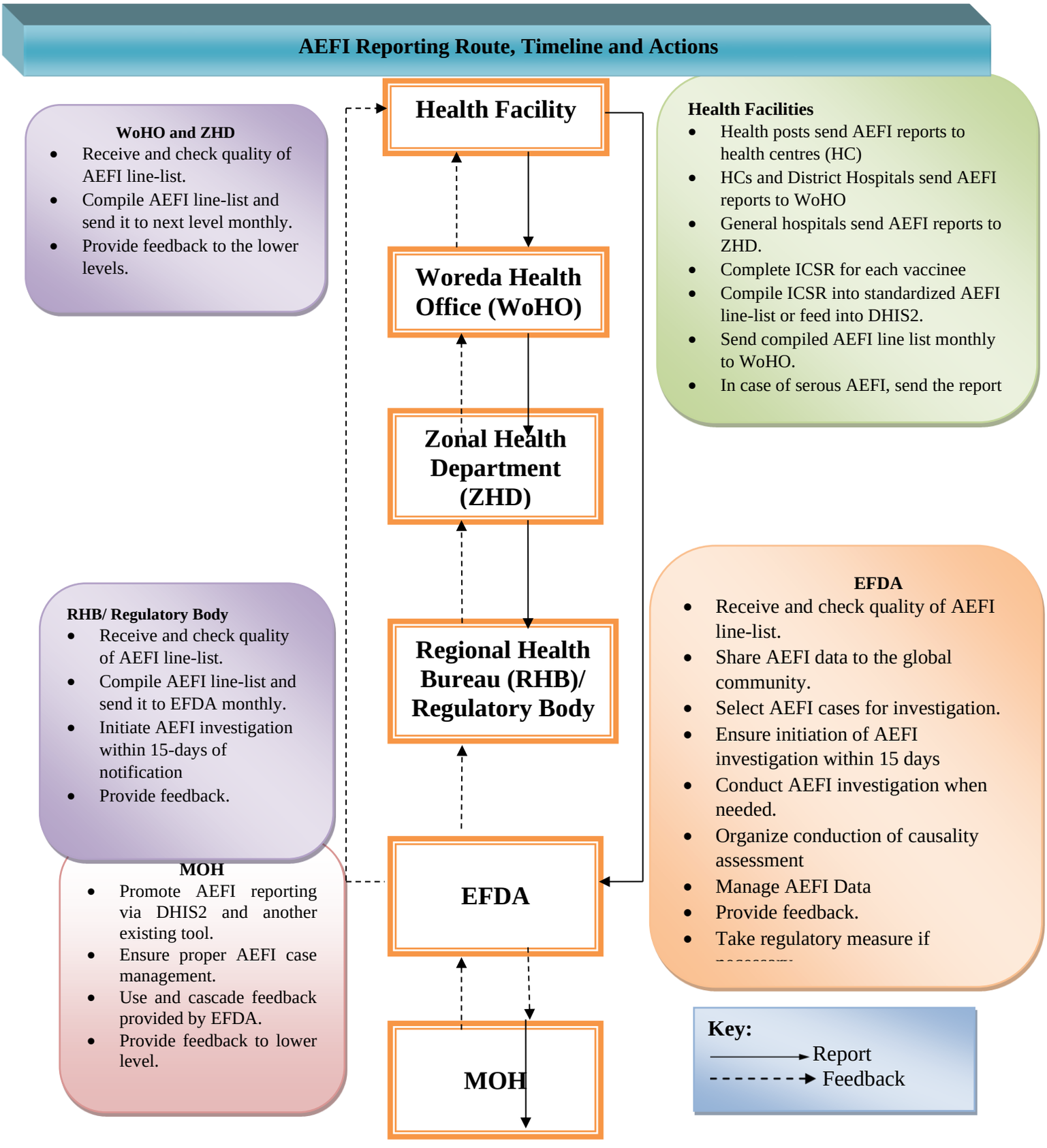
4.3.2. Reporting AEFIs during immunization campaigns

A campaign is an opportunity to strengthen or establish immunization safety surveillance. Proper planning to reduce immunization error-related reactions, to monitor and respond to AEFI can minimize adverse events and their effects during a campaign. Careful planning will limit the potential for negative publicity from an AEFI. During mass immunization or a special immunization programme, it is of utmost importance to ensure AEFI reporting for two reasons:

- Mass immunization and special immunization programmes cover a large number of individuals in a particular target group in a specified time period. Therefore, an excess number of adverse events may be reported within a short time period. The rate of events remains unchanged, but the increased number of events tends to be noticed by both staff and the public, particularly when injectable vaccines are used and at a time of high social mobilization. Unless an event is properly investigated or analysed, it can cause concern among the public and also may affect the immunization programme.
- During special immunization programmes, 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 strengthening surveillance during special immunization programmes.

4.3.2.1. To whom to report?

Health professionals complete and submits an AEFI form to the health facility's EPI Coordinator. The report is then submitted to the next higher administrative level and finally all the reports should be submitted to EFDA as shown in the diagram below (Fig. 2).


AEFI Reporting Route, Timeline and Actions
Health Facility
Woreda Health Office (WoHO)
Zonal Health Department (ZHD)
Regional Health Bureau (RHB)/ Regulatory Body
EFDA
MOH
WoHO and ZHD
Receive and check quality of AEFI line-list.
Compile AEFI line-list and send it to next level monthly.
Provide feedback to the lower levels.
Health Facilities
Health posts send AEFI reports to health centres (HC)
HCs and District Hospitals send AEFI reports to WoHO
General hospitals send AEFI reports to ZHD.
Complete ICSR for each vaccinee
Compile ICSR into standardized AEFI line-list or feed into DHIS2.
Send compiled AEFI line list monthly to WoHO.
In case of serous AEFI, send the report
RHB/ Regulatory Body
Receive and check quality of AEFI line-list.
Compile AEFI line-list and send it to EFDA monthly.
Initiate AEFI investigation within 15-days of notification
Provide feedback.
EFDA
Receive and check quality of AEFI line-list.
Share AEFI data to the global community.
Select AEFI cases for investigation.
Ensure initiation of AEFI investigation within 15 days
Conduct AEFI investigation when needed.
Organize conduction of causality assessment
Manage AEFI Data
Provide feedback.
Take regulatory measure if
MOH
Promote AEFI reporting via DHIS2 and another existing tool.
Ensure proper AEFI case management.
Use and cascade feedback provided by EFDA.
Provide feedback to lower level.
Key:
Report
Feedback

4.4. Investigating AEFIs

Investigation of an AEFI report is critical to identify and correct the problem(s)as well as to ensure trust among clients and different Expanded Programme on Immunization (EPI) actors. During an investigation, evidence, information, and documents will be collected for further action. The goal of an investigation is to collect further information about the cases for causality assessment.

The most important pre-requisite of an AEFI case investigation is to frame a diagnosis of the case based on history, clinical examination, study of documents and reports and field visit. The findings of the investigation may lead to appropriate action and prevent further AEFIs. Investigation should identify any immunization related errors because these are preventable. If co-incidental events are recognized, proving them will be important to maintain public confidence in the immunization program.

4.4.1. Objectives of AEFI investigation

The goal of an AEFI investigation is to search for detailed information of an adverse event and take appropriate corrective actions when necessary to maintain public confidence in the immunization program. The specific objective of an AEFI investigation is to:

- Confirm the reported diagnosis or establish a diagnosis.
- Document the outcome of the reported adverse event.
- Identify the details of vaccine (s) administered and to determine the timing between administration of the vaccine and the onset of the event.
- Examine the operational aspects of the program. Even if an event seems to be vaccine induced or coincidental, immunization related errors may have increased its severity.
- Determine whether a reported event was a single incident or one of a cluster and if it is a cluster where the suspected immunizations were given and what vaccines were used.
- Determine whether similar events are occurring in individuals who have not received the same vaccine.
- Address parent/community concerns.
- Generate new hypotheses about vaccine reactions that are specific to the population.
- Identify the cause of AEFI if possible.

4.4.2. What should be investigated?

The following medical incidents, i.e., trigger events, should be investigated.

- All serious AEFI cases
- Clusters and events above the expected rate and severity
- Suspected signals/previously unrecognized event associated with an existing or newly introduced vaccines.
- Suspected immunization error
- Significant events of unexplained cause within plausible time of vaccination
- Events causing significant parental and community concerns AEFI that appears on the list of events defined for AEFI surveillance.
- Any unexpected adverse event following vaccination should be reported and investigated irrespective of the time interval between vaccination and onset of symptoms.

4.4.3. Who should be involved in AEFI investigation?

AEFI investigation taskforce is established in each region which is composed of representatives from regional EPI, regulatory body, Public Health emergency management, pharmacy service, EFDA branch office. The AEFI investigation taskforce is responsible to conduct AEFI case investigation in their respective regions. EFDA, national PV advisory committee, National EPI and development partners will provide support as needed. When there is a gap for an investigation to be conducted by the regional AEFI investigation taskforce, team of experts from the national level will conduct the investigation.

4.4.4. When to investigate?

The urgency of the investigation will depend on the situation. However, investigation should begin within fifteen days of notification to the EFDA. Early AEFI case investigation helps to identify any possible immunization error(s) that might be present and correct them before other people are exposed to the same error, and to show members of the community that their health concerns are taken seriously.

4.4.5. How to investigate?

Every preparation that needs to be done should be done before beginning data collection. Furthermore, it is important to notify all parties involved. An AEFI investigation follows standard epidemiological investigation principles. In addition, investigation of the vaccine(s), administration techniques and procedures, and service in action should be conducted. All necessary data should be collected during AEFI investigation by using standard AEFI investigation form (Annex II). The investigation task force should:

- Obtain information from patient or relatives directly/ use available records.
- Obtain information from immunization service providers and medical care service providers (hospital staff)/ use available records.
- Ask about the vaccine(s) administered and other drugs potentially received.
- Establish a more specific case definition if needed.
- Ask about other vaccines who may have received the same or other vaccines.
- Observe the service in action.
- Ask about cases in unvaccinated persons.
- Formulate a hypothesis as to what may have caused the AEFI.
- Collect specimens (if indicated by investigation, but not as a routine):
    - from the patient
    - the vaccine and diluent if applicable
    - the syringes and needles
- Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

It is important to investigate suspected adverse events promptly and completely. During the investigation process, the investigation team should communicate with all concerned parties on process of investigation without suggesting the cause. The investigation task force should follow the following steps while conducting the investigation (Table 10).

Table 10: Steps of AEFI Investigation and actions taken at each step.

Steps	**Actions**
1) Confirm information in report	• Obtain patient's medical file (or other clinical record) • Check details about patient and event from medical file and document information. • Obtain any details missing from AEFI Report Form. • Identify any other cases that need to be included in the investigation
2) Investigate and collect data: About the patient:	• Immunization history • Previous medical history, including prior history of similar reaction or other allergies. • Family history of similar events
	• History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event

About the event: About the suspected vaccine(s): About other people:	• Treatment, whether hospitalized, and outcome
	• Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor, and temperature record of refrigerator. • Storage of vaccine before it arrived at health facility, where it has come from higher up the cold chain, vaccine monitor card.
	• Whether others received the same vaccine and developed illness • Whether others had similar illness (may need case definition); if so exposure of cases to suspect vaccine(s) • Investigate the local immunization service
3) Assess the service by: Asking about:	• Vaccine storage (including open vials), distribution, and disposal. • Diluent storage and distribution • Reconstitution (process and time kept) • Use and sterilization of syringes and needles. • Details of training in immunization practice, supervision and vaccinator(s) • Number of immunizations greater than normal?
Observing the service in action:	• Refrigerator-what else is stored (note if similar containers stored next to vaccine vials which could be confused); which vaccines/diluents stored with other drugs; whether any vials have lost their label. • Immunization procedures (reconstitution, drawing up vaccine, injection technique, safety of needles and syringes; disposal of opened vials) • Do any open vials look contaminated?
4) Formulate a working hypothesis	• On the likely/possible cause(s) of the event.
5)Test working hypothesis	• Does case distribution match work hypothesis? • Occasionally, laboratory tests may help. • If program related errors are working hypothesis, correct them. • Vaccine problems suspected, quarantine suspect vaccines
6)Conclude investigation	• Reach a conclusion on the cause/propose the possible cause. • Complete AEFI Investigation Form

	• Take corrective action, and recommend further action

4.4.6. Investigation of AEFI with fatal outcome

In the event of an identified death following immunization, the field investigation has to be initiated immediately. All administrative levels including the national immunization program should be notified of the death. As any fatality temporally linked to a vaccination can cause panic, the public will also demand an immediate explanation thus an investigation has to be conducted without any delay. A postmortem examination(autopsy)is preferred and recommended following all deaths suspected to be caused by a vaccine / immunization. However, the decision to conduct a post-mortem should be within the religious, cultural acceptance and legal framework of the country. If autopsy is not possible verbal autopsy can be carried out.

4.4.7. Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administered. Apart from checking on these three factors, the investigators should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease. Cluster investigation begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition. The investigators should demarcate the cluster and identify common exposure factors within the cluster. Cluster identification (i.e. cases with common characteristics) are done by gathering details (Who, when and where) of vaccines administered. This can be achieved by collecting and recording:

- Detailed data on each patient.
- Program-related data (storage and handling, etc.); and
- Immunization practices and the relevant health professionals' practices.

Common exposures among the cases can be identified by reviewing:

- All data on vaccine(s) used (name, lot number, etc.).
- Data on other people in the area (also non-exposed); and
- Any potentially coincident factors in the community.

When an AEFI cluster has been identified, the cause-specific definitions provide a framework for investigation and causality assessment. Usually, the key considerations will be to investigate the possibility of an immunization error, vaccine reaction or a vaccine quality defect. For relatively new vaccines or established vaccines used in new target population, a cluster may represent a previously unrecognized vaccine product related reaction. Awareness of vaccine reaction rate and

background rate of reported event is essential for assessing a cluster in terms of the strengthen of the signal it may provide (Fig. 3).

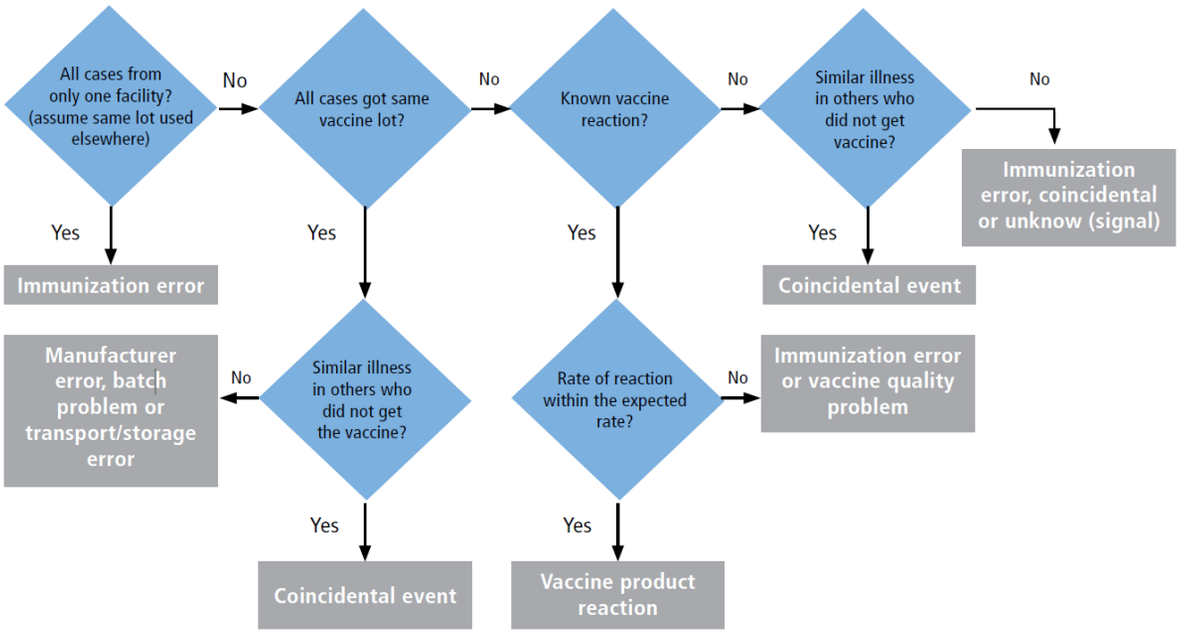


Figure 3: Identifying cause of AEFI cluster.

The possibility of immunization error must be considered when events cluster in one setting without a similar change in frequency in other settings using the same vaccine. On the other hand, if an increased frequency of events is reported from multiple settings the possibility of a quality defect must be considered more strongly. Clusters of fainting after immunization are well-recognized immunization anxiety-related reactions during immunization programs targeting adolescent girls.

4.4.8. Laboratory testing of specimens

Laboratories have an important role in AEFI case diagnosis and case management. They also have a key role in testing the quality of the samples of vaccines and the supplies used. Laboratory tests for the purpose of AEFI case diagnosis and case management conducted on the patient (e.g. blood, urine, radiology, ECG etc) are based on the provisional case diagnosis and recommendations of the treating physician. These tests are considered “routine” and should be performed in clinical laboratories. The results of these tests are important to confirm the case diagnosis and arrive at the “valid diagnosis” for assessing causality.

Laboratory testing of samples of vaccines and supplies are rarely necessary. Laboratory testing may sometimes confirm or rule out the suspected cause: the vaccine may be tested for sterility and adjuvant (e.g. aluminium content); the diluent for sterility and chemical composition; and the

needles and syringe for sterility. Testing should be requested on a clear suspicion and not as routine, and never before the working hypothesis has been formulated. Determining which samples to send, if any, depends on the working hypothesis for the cause of the event(s) (Table 11). If the used vial of suspect vaccine is available, it should be sent with unused vials of the same lot.

Table 11: Laboratory testing to investigate AEFIs by working hypothesis.

Working hypothesis: programme error is suspected	Specimen to send	Laboratory test
Vaccine transportation or storage	Vaccine vial	Composition
Reconstitution error	Vaccine vial and/or diluent	Sterility or composition (chemical)
Non-sterile injection	Needle, syringe, vaccine vial and diluent	Sterility
Vaccine problem	Vaccine vial	Composition

4.5. AEFI causality assessment

Causality assessment of AEFI is a vital component of AEFI risk assessment, decision-making and the initiation of action. Causality assessment is the systematic evaluation of the information obtained about an AEFI to determine the likelihood that the event might have been caused by the vaccine/s received. Causality assessment does not necessarily establish whether or not a definite relationship exists, but generally ascertains a degree of association between the reported adverse events and the vaccine/vaccination. Nevertheless, causality assessment is a critical part of AEFI monitoring and enhances confidence in the national immunization programme. Vaccine recipients want to know whether they experienced the event due to the vaccine. They may believe that because one event followed another, it was causal. It may be difficult to explain that that this might not have been the case. Causality assessment may provide a more descriptive explanation that may reassure the vaccine and lead to better management of the event that ultimately helps the vaccinee. In essence, determining whether or not an AEFI is attributed to the vaccine or vaccination decides the steps needed to be taken to address the event. Causality assessment is important for:

- Identification of vaccine-related problems.
- Identification of immunization error-related problems.

- Excluding coincidental events.
- Detection of signals for potential follow-up, testing of hypothesis and research; and
- Validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

The quality of the causality assessment depends on three factors:

- The performance of the AEFI reporting system in terms of responsiveness and effectiveness (the quality of case reporting and follow-up investigation).
- Availability of adequate medical and laboratory services for the investigation and follow-up of cases, and access to background information on population disease/illness rates in the absence of vaccination; and
- The quality of the causality review process, including access to appropriate expertise.

4.5.1. Levels of AEFI causality assessment

Causality assessment of AEFI applies to investigating relationships between a vaccine and an adverse event at three levels - the population level, the level of the individual AEFI case report, and in the context of the investigation of signals – all of which depend on an assessment of causality for individual cases.

Individual AEFI case report: The aim is to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to use of the vaccine. The aim of causality assessment at the individual level is to address the question "Did the vaccine given to a particular individual cause the particular event reported?" It is usually not possible to establish a definite causal relationship between a particular AEFI and a particular vaccine on the basis of a single AEFI case report.

Population level: Using surveillance data and an appropriate statistical methodology in order to test the hypothesis that there is a causal association between the usage of a vaccine and a particular AEFI. This may sometimes be combined with causality assessment at the individual level (of AEFIs collected within that system) whereby some or all of the cases of interest could undergo individual case review and causality assessment before inclusion in a group analysis.

Investigation of signals: The assessment of whether a particular vaccine is likely to cause a particular AEFI takes into account all evidence from individual AEFI cases, surveillance data and, where applicable, cluster investigations as well as nonclinical data. A review of the corresponding adverse event reports should be performed to verify that the available documentation is strong enough to suggest a new potential causal association, or a new aspect of a known association, in order to justify further evaluation of the signal. The objective of signal

evaluation is to draw conclusions on the presence or absence of a suspected causal association between an adverse event and a vaccine, and to identify the need for additional data collection or for risk minimization measures. This may also prompt the regulatory authorities to request the marketing authorization holder (MAH) for an additional analysis of its available data on a particular event under investigation.

4.5.2. Criteria for causality in the causality assessment process

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

- **Temporal relationship**: Exposure to the vaccine must precede the occurrence of the event. Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must always precede the occurrence of the disease. This is the only absolutely essential criterion of causality.
- **Biological plausibility**: Biological plausibility may provide support for or against vaccine causality. In other words, the association should be compatible with existing theory and knowledge related to how the vaccine works.
- **Strength of the association**: The stronger the (statistical) association, the more likely that the relation is causally associated.
- **Consistency of the association**: The association is consistent when results are replicated in studies in different settings, among different populations and using different methods.
- **Specificity**: The vaccine is the only cause of the event that can be shown.
- **Definitive proof that the vaccine caused the event**: There is clinical or laboratory proof that the vaccine caused the event. Consideration of alternative explanations: In doing causality assessment, all reasonable alternative etiological explanations need to be considered.
- **Prior evidence that the vaccine in question could cause a similar event**: The concept of "re-challenge" is more commonly used in medicine causality, but it has also been helpful for certain vaccine-event considerations (e.g. Guillain-Barré syndrome or GBS occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine).

4.5.3. Who should do causality assessment?

To ensure that the prerequisite criteria described above are met and to ensure broader acceptance of the findings, causality assessment of AEFI should ideally be performed by a reviewing team or committee of reviewers whose areas of expertise could include paediatrics, neurology, general

medicine, forensic medicine, pathology, microbiology, immunology and epidemiology. Other external experts should be invited for the review of specific events. Causality assessment in Ethiopia is done by the National Pharmacovigilance Advisory Committee (NPAC), that is:

- Independent
- Free of real or perceived government, and industry conflicts of interest
- Has broad range of expertise in the areas of 'infectious diseases, paediatrics, epidemiology, microbiology, pathology, immunology, neurology, cardiology, internal medicine, pharmacology, clinical pharmacy and other relevant fields.
- The committee has written Terms of Reference (TOR) and decides independently but having a support and close communication with EFDA.

4.5.4. Case selection for causality assessment

The selection of cases for causality assessment should focus on:

- Serious AEFI, as per the regulatory definition of serious
- The occurrence of events above an expected rate or of unusual severity
- Cluster of events
- Signals generated as a result of individual or clustered cases as these could signify a potential for large public health impact.
- Other AEFI as decided by the review committee or an investigation team such as immunization errors, significant events of unexplained cause occurring within 30 days after a vaccination (not listed in the product label), or events causing significant parental or community concern.

4.5.5. Prerequisites/ basic requirements for causality assessment

Timely reporting of AEFI followed by appropriate and detailed investigation are important. The information and evidence that is collected during a good quality AEFI investigation holds the key for a successful evaluation of the event, the circumstances of its occurrence and provides vital clues for the probable cause of its occurrence. An AEFI should fulfil four prerequisites before causality assessment, namely:

- The AEFI case investigation should have been completed. Premature assessments with inadequate information could mislead the classification of the event.
- All details of the case should be available at the time of assessment. Details should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.

- There must be a "valid diagnosis" (as explained below) for the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease in question.
- All vaccines and medicines that were administered before the event should be identified.

4.5.6. Steps for causality assessment of AEFI

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

Step 1: Eligibility: To determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.

Step 2: Checklist: To systematically review the relevant and available information to address possible causal aspects of the AEFI (Annex III)

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

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

WHO has developed an e-tool that will help assessors perform an AEFI causality assessment both online and offline modes. Details are available at http://www.who.int/vaccine_ safety/causality-assessment-software-EN/en/.

Step 1: Eligibility

To proceed with causality assessment, it is necessary to first confirm that the vaccine was administered before the event occurred. This can be ascertained by eliciting a careful history with the relevant stakeholders to ascertain the timing of vaccination with the onset of any signs and/or symptoms related to the event being assessed. It is also essential to be clear on the "diagnosis" of the reported AEFI. The valid diagnosis refers to a clinical sign, symptom, abnormal laboratory finding, or disease with clear details as to onset. The diagnosis should also meet a standard case definition for the disease process being assessed. If available, it is best to adopt one of the Brighton Collaboration case definitions. However, if this is not possible, case definitions (Annex IV) can be adapted from the standard medical literature, national guidelines or local clinical practice. If the reported event does not have a valid diagnosis, it may not be possible to adequately categorize the AEFI. Therefore, additional information should be collected to arrive at a valid diagnosis or clear definition of what event is being assessed for causality against the given vaccination. Another important point is that while the revised process envisages the causality assessment of an individual AEFI case with a particular vaccine, in the event of multiple vaccines being given simultaneously, a causality assessment may have to be conducted taking into account each vaccine separately.

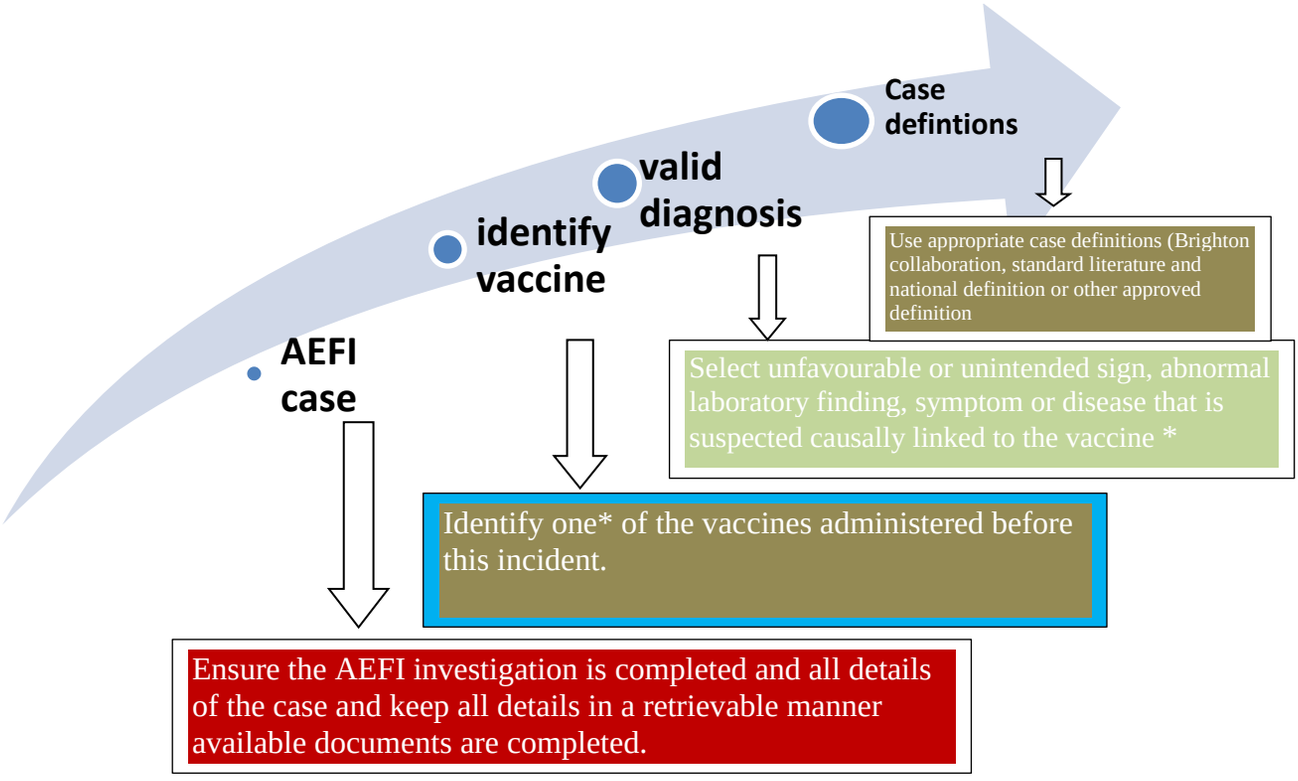


Figure 4: Case's eligibility for causality assessment.

***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 reviewer should consider doing a separate causality assessment for each diagnosis. Likewise for a cluster of AEFI, each individual case must be assessed separately.*

If the investigated AEFI appears to not meet the eligibility criteria because of inadequate information, attempts should be made to collect any additional information required in order to ensure that the case can be properly assessed for eligibility. Additionally, all cases reported (including those deemed or eventually deemed ineligible cases) should be stored in a repository (preferably electronic) so that they can be accessed should additional information become available through reports of similar cases, new evidence in the literature, or through periodic database analysis. At the successful completion of this stage, the committee should define the "causality question" as below.

Has the_____vaccine /vaccination caused_____ (Valid Diagnosis)?

Step 2: Checklist

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

- Is there evidence for other causes?
- Is there a known association with the vaccine/vaccination in the medical literature? If so, did the event under assessment occur within an appropriate time window and, if so, was it associated with the vaccine product, an immunization error or immunization-related anxiety.
- Is there any strong evidence against a causal association?
- Other qualifying factors for classification (e.g. background rate of the event, present and past health condition, potential risk factors, medication, biological plausibility, etc). Once the checklist (Annex III) is systematically completed, the answers in the checklist are applied to the algorithm.

Step 3: Algorithm

After the checklist is completed, data related to the association under investigation is ready to be applied to the algorithm (Fig. 5). The algorithm aims to be a roadmap for the decision-making of the reviewers, but it does not, and should not, take away the expert and deductive logical process inherent in linking a diagnosis to its potential cause. The stepwise approach of the algorithm helps to determine if the AEFI could be consistent or inconsistent with an association to immunization, an indeterminate outcome or unclassifiable.

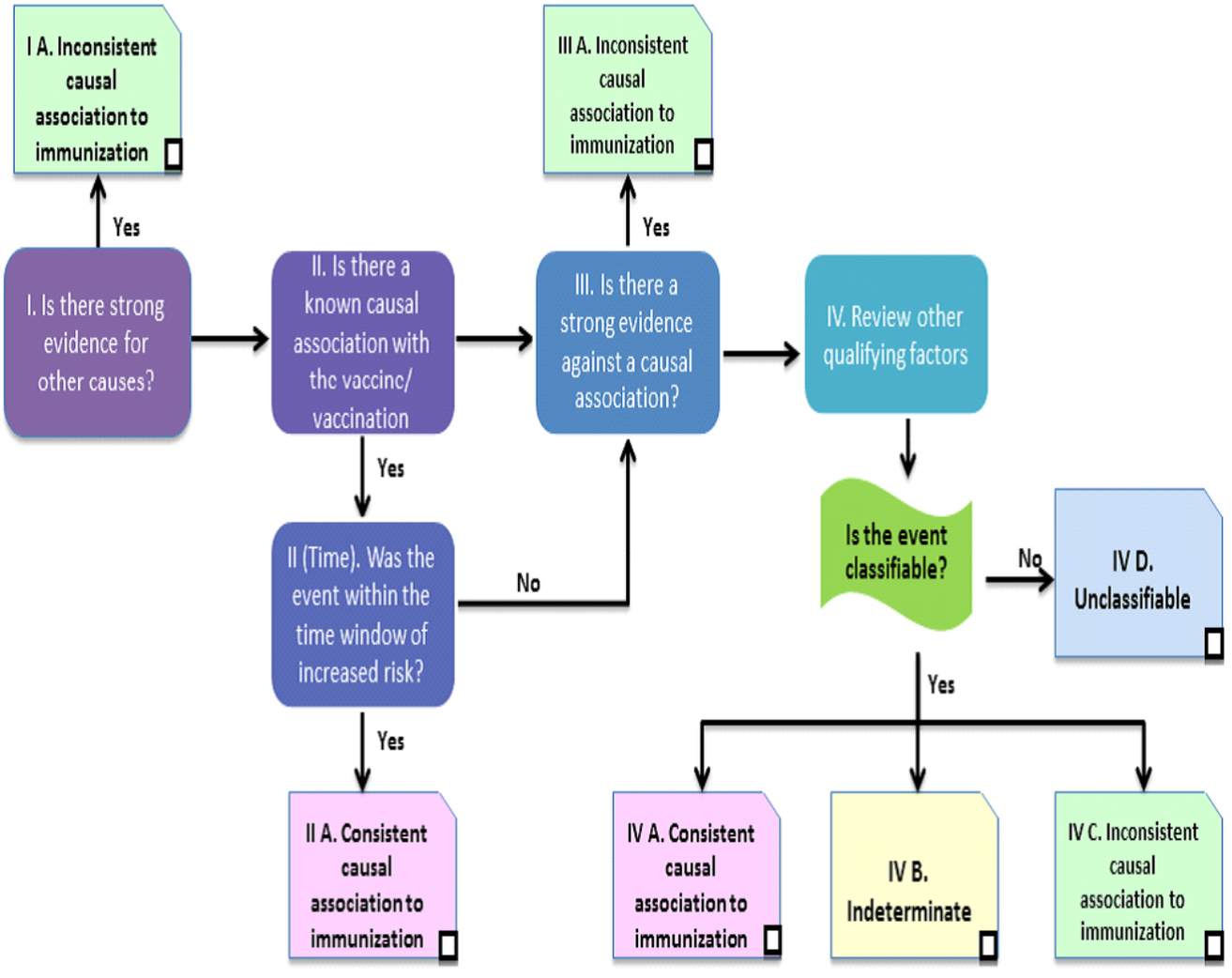
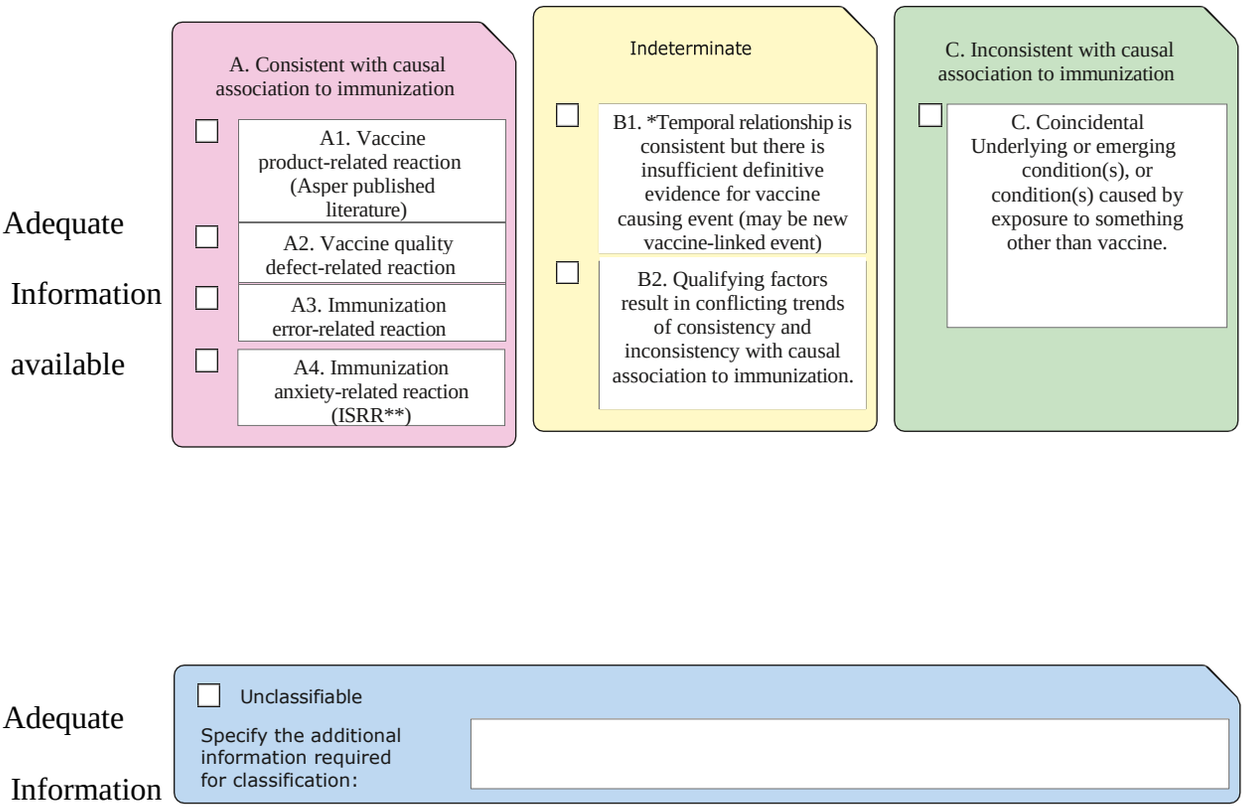


Figure 5: Causality assessment algorithm.

Step 4: Classification

The final classification is based on the availability of adequate information. The cause-specific definitions provide clarity on "A. Consistent causal association to immunization" and "C. Inconsistent causal association to immunization" (coincidental). The association is considered "B. indeterminate" when adequate information on the AEFI is available but it is not possible to assign it to either of the above categories. The details are presented in Fig. 6.



*

**B1: Potential signal and maybe considered for investigation*

*** Immunization stress related*

Figure 6: Causality assessment classification.

4.5.7. Actions to be taken after causality assessment.

Determining causality is not an end in itself. The lessons learned should provide insights and way forward for the technical, immunization program staff working at woreda, zonal and higher level. Findings should be promptly and clearly communicated and the messages should be clear on any next steps to be taken, including communicating reassurance or the need to take action around the

program including training, research, modifying systems, refining tools and revocation of marketing authorization and recall of the vaccine and so on to avoid and/or minimize recurrences. Based on global guidelines, EFDA and the EPI will take the following actions depending on different causality conclusion resulting from the assessment.

A. Consistent causal association to immunization

A1. Vaccine product-related reaction

In vaccine-related reactions, decisions should be carefully thought out and the impact on the immunization program, alternate sources of vaccine, and the reliability of the evidence on which the decision is based needs to be carefully examined. Communication with the vaccine manufacturer, UNICEF and WHO should be made before making any decision with regard to the vaccine withdrawal.

A2. Vaccine quality defect-related reaction

If this reaction is related to a particular lot or batch, the distribution of the lot or batch has to be ascertained and specific instructions must be provided on the utilization or non-utilization of the lot or batch. It is important to inform the EFDA, the marketing authorization holder and global partners such as WHO and UNICEF about the AEFI.

A3. Immunization error-related reaction

Training and capacity-building are critical to avoid recurrences of such reactions. Supervision and follow up is also required.

A4. Immunization anxiety-related reaction

Depending on the solitary or cluster nature of the immunization anxiety-related reaction there are separate approaches for prevention. Vaccination should take place in an ambient and safe environment.

B. Indeterminate

B1. Consistent temporal relationship but insufficient evidence for causality

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

B2. Conflicting trends of consistency and inconsistency with causality

These cases are classified on the basis of available evidence. If additional information becomes available, the classification can move into a more definitive category. During the assessment, the

reviewers should clarify what additional information would be helpful to finalize the causality assessment and should seek information and expertise from national or international resources. The Global Advisory Committee on Vaccine Safety (GACVS) can be approached for guidance through WHO, particularly when an event is likely to impact the immunization programme significantly.

C. Inconsistent causal association to immunization (coincidental)

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

D. Ineligible cases and Unclassifiable cases

Cases ineligible for causality assessment are those where the amount of information available to the assessor is limited such that a causality question cannot be created. For example, the reviewer does not have information on the type of vaccines administered to the patient or the clinical details are insufficient to formulate a causality question. Cases may also be considered ineligible prior to the assessment if the investigation is incomplete, and the essential information is not available.

Unclassifiable cases occur in instances where the reviewer is able to formulate a causality question, but during the process of assessment discovers that some important elements are missing to enable a logical classification. For both ineligible and unclassifiable cases, it is important to specify the missing elements and make attempts to obtain the information so that causality assessment could be attempted again. It is essential that the available details of such cases are placed in a central repository that the investigators can revert back to when additional information that would help with the causality assessment is available. If AEFI causality is not established, depending on the nature of the event, its extent and whether it is on-going, a further investigation or epidemiological study may be warranted. However, it must be accepted that in some cases the relationship to vaccine will never be clear.

4.6. Action and response to AEFI

Considering the situation or event, responding to AEFI may be immediate short-term activities or/and long-term follow-up activities. Follow-up activities should be based on findings of investigations, causality assessments and recommendations by the investigation/expert committees. Major follow-up actions may have an impact on the national immunization programme, as well as on regional and global programmes and planning.

4.6.1. Patient care

It is of utmost importance to ensure that proper and early treatment is received by affected vaccinees (patients), regardless of the diagnosis. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. Health professionals need to know how to recognize AEFI, how to treat them or refer them to a clinician/hospital and must report AEFI as soon as possible. Concomitantly with the patient management these cases should be documented in the AEFI case reporting form and reported to the responsible body.

4.6.2. Follow-up actions

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization 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 (Table 12). However, it must be accepted that in some cases the relationship to vaccine will never be clear. Communication and training are two important follow-up actions that have long term implications.

Table 12: Actions to be taken upon completion of the investigation/causality assessment.

Type of AEFI	**Follow-up action**
Vaccine-related reaction	If there is a higher reaction rate than expected from a specific vaccine or lot, EFDA should obtain information from the manufacturer and consult with the WHO and UNICEF to consider: • withdrawing that lot. • investigating with the manufacturer. • Obtaining vaccine from a different manufacturer.
Immunization error related	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 professionals. • Intensifying supervision. 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-related error and, that the most likely explanation is a temporal association between the event and vaccine/vaccination. This communication can be challenging when there is widespread belief that the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to ensure that the event was truly coincidental. The potential for coincidental events to harm the immunization program through false attribution is immense.

Communication and training are two important follow-up actions that have long-term implications. They should not necessarily be focused on an individual event, but they should emphasize the need for programme managers and others involved in immunization to pay attention.

4.6.3. Logistics

Immunization supply chain, injection safety and waste management are part of immunization safety surveillance. It is highly recommended to improve supply chain system and ensure safe injection practices. The EPI, Ethiopian Pharmaceuticals Supply service (EPSS) and EFDA needs to plan and work harmoniously to improve the immunization safety surveillance system. Improving logistics will be the appropriate response in regard to program errors that can be traced to the lack of supplies or equipment or to a failure in the cold chain or inadequate skills.

5. AEFI Data Management

The AEFI data management system involves all courses from data generation to having the analysed or synthesized information for action and/or appropriate communication. AEFI data and its proper management is important at all levels. AEFI surveillance should include structured, systematic and permanent data collection on the safety of vaccines used in the country's immunization program. Managing the collected data is one of the basic components of the AEFI surveillance system. The data management cycle starts from the source of AEFI data and ends with provision of feedback, as depicted below:

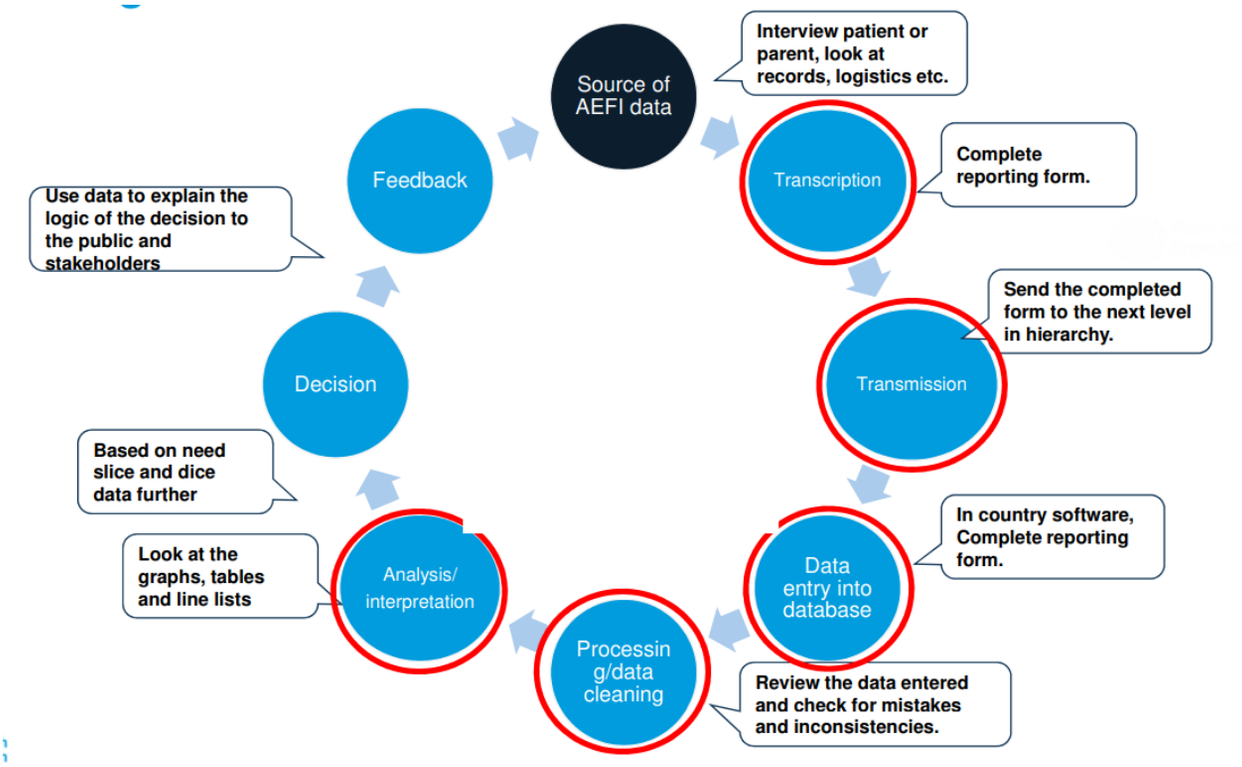


Figure 7: Data management cycle.

5.1. Sources of AEFI data

Information on vaccine safety and the possible occurrence of AEFIs can be obtained from clinical examinations, interviews of health professionals, care givers and community leaders, review of charts and registers (ANC, OPD and Immunization), vaccine and vaccine supplies ledger, observation of immunization administration, sub-national PV centres, vaccine handling and storage and diagnostic reports (laboratory reports, imaging reports, etc…). Management of data on AEFIs consists of reviewing data from the following sources:

- Individual case safety report (individual AEFI report)
- Data collected into a line list (Annex V)
- Case investigation forms
- Laboratory information (Human and vaccine related)
- Records about similar events in the community
- Records of the implicated vaccine and vaccine related supplies
- Review of published information from journal/article
- Data from Medicine Regulatory agencies

5.2. Data entry

Data entry is expected to occur at health facility, woreda/zonal, regional and national PV centres for AEFIs detected during immunization. Data entry can be affected using common electronic tools; e-reporting/web-based reporting and Med Safety mobile app. Data received through hard copy, email and line list will be entered at regional and national PV centres using Vigiflow. In this regard, to avoid duplication of data at all levels, an effort has to be made while compiling and submitting the report including notification of the primary reporter to the next higher level. AEFI data should be entered as soon as possible at all levels. However, during campaigns, overall data entry may be performed on completion of surveillance, investigation and post-campaign survey activities. All reporting forms and other data-collection tools completed during the investigations and surveys shall be submitted to the central level with copies kept at various levels.

5.3. Data Analysis and Interpretation

Before analysing an entered AEFI data, it will be cleaned and validated at all levels in order to ensure data quality. All reported AEFI cases should be line-listed at all levels using the AEFI line-list which enable us to get the aggregate data which is the first step of data management. Basic time, place and person analysis should be done by the woreda/zone and regional program managers. Other key analysis areas that relate to the performance of the surveillance system at all levels include.

- Reporting source (reports of AEFI by different sources may provide a wider range of information)
- Completeness of submitted AEFI forms.
- Verification and reassurance of data accuracy
- Identifying health institutions where AEFI are not reported (determining whether this is due to failure of reporting or whether there are no AEFI to be reported) and checking on “zero reporting” or “nil reporting”.
- Performance of investigated cases (except in health facilities)
- Performance of causality assessment to classify the AEFI (mandatory for national)
- Estimated AEFI reporting rates (assessing the number of reported AEFI and the rate per 1000, 10, 000 or 100, 000 doses of vaccine used in a specified time period).
- Estimated rates by type of AEFI and by antigen (assessing the number of cause specific reported AEFI and the rate for 1000, 10 000 or 100 000 doses of vaccine used in a specified time period).

- Comparison of the observable rates with available or expected known events, whether vaccine reactions or background rates or historic reporting trends (mandatory for national level)

5.3.1. Responsible body for data analysis at different levels

Prior to the analysis of the line list at the national level, it is important to re-check the case definitions adopted by the reporting sources. The case should fit into a case definition such as the Brighton collaboration case definitions or any definition selected by the National Pharmacovigilance Advisory Committee. Data analysis could be carried out by the responsible focal persons at different levels in the vaccine safety surveillance system. Analysis of data at woreda/zonal level is important to identify programme errors. This helps to take corrective action in a timely manner. Table 13 below describes the type of analysis and the purpose.

Table 13: Types and purpose of data analysis at different levels.

Program implementation level	**What data to analyse**	**Purpose of data analysis at given level**
Local level (Immunization provision level)	Number of reports clinics, hospitals, villages by a given time	These are program operation/surveillance performance indicators (timeliness, completeness)
	Reported AEFIs by place. (clinics, hospitals), persons and time	Identification of immunization related errors will lead to corrective action
	Reported AEFI by antigen	Will identify vaccine reactions and coincidence
Sub national level (Regional/ zone/ woreda)	Number of reports by local levels	These are program operation /surveillance performance indicators (timeliness, completeness) at local level.
	Reported AEFI by place. (clinics, hospitals), persons and time	Identification of immunization related errors will lead to corrective action
	Cluster analysis	Cluster analysis leads to identify immunization related errors, coincidence and vaccine reactions

	Reported AEFI by antigen	Will identify vaccine reactions and coincidence
National level	Number of reports by intermediate levels	These are program operation /surveillance performance indicators (timeliness, completeness) at intermediate level
	Reported AEFI by place (clinics, hospitals), persons and time	Will identify vaccine reactions, including signals detection.
	Cluster analysis	Cluster analysis leads to identify immunization related errors, coincidence and vaccine reactions
	Reported AEFI by antigen	Leads to taking operational and policy decisions in the country

Investigation data analysis consists of reviewing the case investigation report for each client, reviewing other data about the event (such as immunization practices at session sites and vaccine lot numbers and expiration dates) and the community in which it took place, making a final diagnosis, and identifying the probable cause. It might not be possible to make a diagnosis, the cause might not be evident, or there might be more than one cause. However, the investigation team should try to collect as much information as they can from the data.

The number of vaccine product-related reactions will naturally increase with increased vaccine use, so it is essential to calculate antigen (vaccine) specific adverse reaction reporting rate. In considering concerns with specific lots, it is important to have accurate denominator of vaccine use as possible, as it is always the rate and not the number of reports that needs evaluation (comparison with known vaccine product-related rates).

5.3.2. Steps in AEFI data analysis and interpretation

Step 1: All reported AEFI cases should be line listed.

Line listing will help for initial identification of clusters or any unusual or significant reported events that need further analysis.

Step 2: Tabulating AEFI data by place, person, time, antigens, and type of events

This step further filters the AEFI by different variables and helps program managers to generate clues for further analysis. Even at this step, it is possible to identify common immunization errors.

For example, increased number of abscesses at an immunization centre is more likely due to immunization error. However, further investigation of such observation is necessary to verify the causality.

Step 3: Calculating AEFI rates.

Number of doses administered for each antigen is the denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year). Analysis shall expand to the AEFI rates by first or second or third dose, when the antigen is administered more than once. For this, the number of doses administered of the given antigen by first, second or third doses need to be used as the denominator.

For example, in region X, registered under-1 year child population is 5000. The coverage of measles vaccine is 90%. During the same year, 20 febrile seizures were reported following measles vaccination. How to calculate rate of febrile seizures? The numerator for this vaccine reaction (febrile seizures) is 20. The most challenging selection is to use a proper denominator. There are a few options for selecting a denominator (Table 14).

Table 14: Options for selecting a denominator.

Denominator	**Limitations**
Administered doses of vaccines	Most reliable, but not often available
Distributed doses	Greater than administered doses, thus may reduce rate (underestimate)
Coverage x population	May be less accurate because of variability in coverage estimates
Target population	Proxy measure for vaccine population (may also underestimate)

Given = Population (<1 yr) = 5000; coverage = 90% and AEFI cases (Febrile Seizure) = 20

In this example, since no other data are available, it can use coverage to get the denominator.

Denominator = Population x coverage = 5000 * 90% = 4500

The reported febrile seizures rate is 20/4500*100 = 0.44%

The use of proper multiplier is important as it may vary by purpose and level of analysis. At local level, percentage (%) is the best choice, whereas sub-national and national levels may use 1000, 100,000 or million as multiplier. For common, minor vaccine reactions, percentage is recommended and for rare and serious reactions, 10,000 (10^4), 100,000 (10^5) or 1 000, 000 (10^6) can be used.

Step 4: Comparison and interpretation of rates

Available expected vaccine reaction rates for each type of AEFI for an antigen (Tables 4 and 5) present a guide to make a decision on corrective action to be taken on reported AEFI. It is also important to know about background rates of reported medical events in the country.

- Background rates are independent and not related with the vaccine.
- Observed (reported) rates include both background rates and vaccine-related rates.

Comparison of background rates with reported rates (observed) of AEFI will lead to a valid conclusion on causality of these events as being due to a vaccine reaction. Based on the above data analysis results, proper interpretation is important for decision making (Table 15).

Table 15: Terminology and interpretation on type of rates.

Terminology	**Definition**	**How is this measured**	**Example**
Background rate	Rate of an event (occurring/ reported/ measured) *due* to all cases fitting the case definition, which are expected to occur in the community in the absence of the putative vaccine.	Background rates can be determined in a population prior to the introduction of a new vaccine or simultaneously in non-vaccinated people.	If we measured the temperatures of a population of 1,000 unvaccinated children for one week, some children would present a fever (defined as >38°C) during the time of observation (e.g., infections). For example, a rate of 2 cases of fever per 1000 children per week.
Observed (reported) rate	This is the background rate PLUS the additional effect of the vaccine.	The observed rate can be measured in pre-licensure clinical trials or post-licensure studies	If we observe the same population of 1000children but we now vaccinate all children and measure their temperatures daily there will be a greater rate of fever. Thus, the rate of fever may

			increase to 5/1000children per week, with the increase concentrated in the 72 hours that follow vaccination.
Vaccine reaction rate (attributable rate).	This is the rate of an event that is caused by the vaccine–that is a vaccine reaction.	Randomized clinical trials which are placebo controlled. Post-licensure studies -passive surveillance.	Thus, the vaccine attributable rate of fever will be 3/1000vaccinated children (that is the observed rate minus the background rate)

The following graphic shows a comparison of the background rate with the observed rate of an event to determine the vaccine reaction rate (i.e. the rate of events that are actually caused by the vaccine)

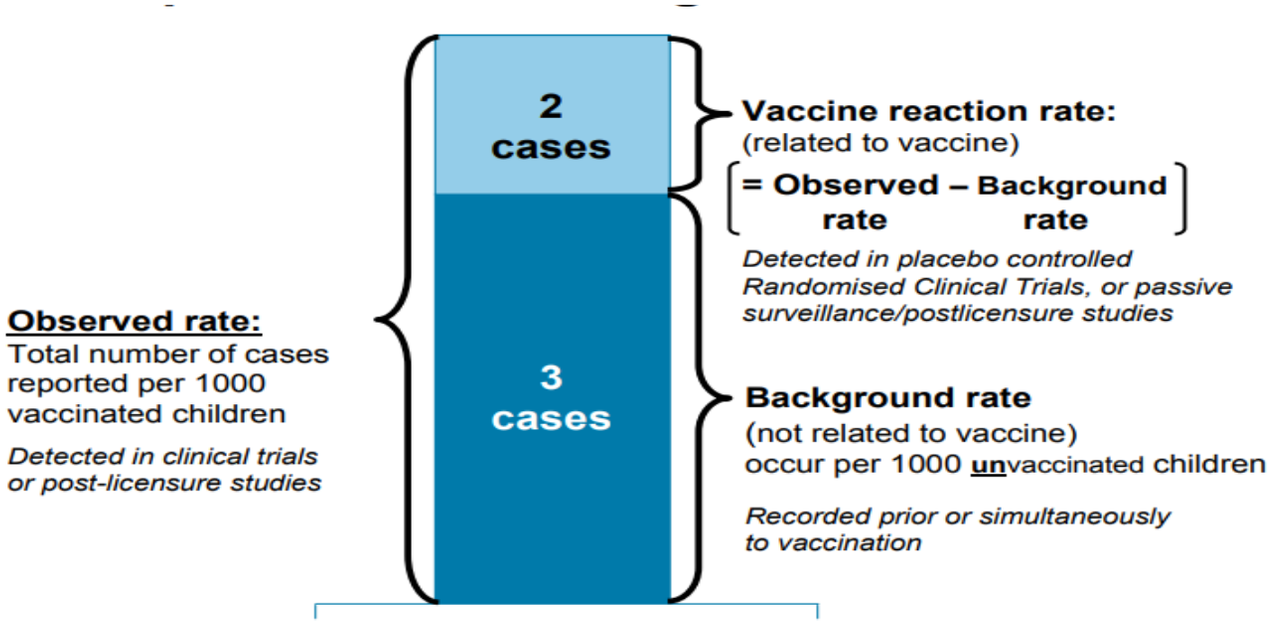


Figure 8: Vaccine reaction rate, observed rate and background rate.

Factors to be considered when comparing rates of AEFIs are summarized in Table 16.

Table 16: Factors to consider when comparing rates of AEFIs.

Vaccines

Although a vaccine may have the same antigens, different manufacturers may produce vaccines (or lots of the same vaccine) that differ substantially in their composition, including the presence of an adjuvant or other components. These variations result in vaccines with different reactogenicity (the ability to cause vaccine reactions), which in turn affects the comparison of their vaccine-attributable rates.

Age

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

Vaccine dose

The same vaccine given as a 'primary dose' may have a different reactogenicity profile than when it is given as a 'booster dose'.

Case definition

Adverse event may be defined differently in surveillance / research studies that do not stick to the same case definition. Not using standardized case definitions may consequently affect the estimation of the AEFI rate. Brighton Collaboration has developed cases definitions for many vaccines reactions.

Surveillance methods

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

Background conditions

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

At all levels, data analysis and interpretation shall be done on monthly basis however during campaign and special concerns, the analysis and interpretation shall be done immediately.

5.3.3. Consideration of causality

Until the investigation is complete a working hypothesis is all that can be formulated. Later it will be possible to analyse the data, assign a cause and classify it into one of the categories of AEFI. For a few medical events, the diagnosis itself will show the cause whether it is immunization error-

related or vaccine-related or coincidental or injection reaction (e.g. injection site abscess). In other cases, additional information may be required as external evidence to identify the cause.

Comparing background data with reported (observed) data does not conclude the causality. It only generates the hypothesis. To conclude that a vaccine causes a particular vaccine reaction, it is necessary to demonstrate that the risk in vaccinated individuals is greater than that in the non-vaccinated, provided that the effects of confounders and bias are ruled out. Estimating relative risk and attributable risk is necessary, and retrospective or prospective analysis of available data or designing epidemiological studies (case series, case-control, cohort or ecological studies) will confirm causality.

Decision and feedback: This is also one part of data management. Decision could be made based on the evidence generated or data transformation while feedback will be provided based on the nature of the case.

Data handling, storage and sharing: AEFI data or information needs not only generation but also management of the data including proper handling or storage. Besides, data security, properly sharing it to the relevant stakeholders and partners in accordance with the requirements stated in the safety data sharing SOP of EFDA requires consideration. Regular and timely sharing of data to the regional and global community is important to maximize resources and capacity for decision making, improves signal detection and identification of very rare events. Data transformation is usually required to facilitate data sharing. As national dashboard of vaccine safety data is important to improve data visibility and facilitate data sharing, EFDA in collaboration with stakeholders should strive to develop and implement. For additional information on monitoring and evaluation aspects of the AEFI surveillance refer to the M & E section of this guideline.

6. Stakeholders in AEFI Monitoring

The EFDA is responsible to ensure that all medicines, including vaccines are safe, effective and of good quality. On the other hand, the EPI program of the MOH is responsible for preventing disease, disability and death by providing safe and effective vaccine to children and adults to prevent and control vaccine-preventable diseases.

AEFI monitoring in Ethiopia needs to be a collaborative effort between the EFDA and various stakeholders, including; the EPI at the MOH, EPHI, regional health bureaus and regulatory bodies, regional and national task forces of AEFI, professional associations, academic institutions, Market Authorization Holders (MAHs) (manufacturers, importers and distributors), health institutions, EFDA and branch offices, Regional PV Centres, EPSS, Health professionals, AEFI Taskforces,

National Pharmacovigilance Advisory Committee, clients including guardians and all concerned local and international development partners.

6.1. Roles and Responsibilities of key stakeholders

6.1.1. MOH/National Immunization Program

- Engage EFDA in the planning, implementation, monitoring& evaluation of EPI.
- Collaborate with EFDA in mobilizing resources to strengthen AEFI monitoring.
- Coordinate the national immunization taskforce/technical working group (TWG) and consider AEFI as priority agenda.
- Collaborate with EFDA in the continuous development, revision and distribution of tools and guidelines for AEFI surveillance.
- Provide capacity building to strengthen the system on AEFI monitoring and case management in collaboration with EFDA.
- Facilitate and ensure AEFI case management at healthcare facilities.
- Provide support to regions, zones and woredas on AEFI monitoring.
- Share AEFI reports received from routine immunization and campaigns with EFDA.
- Ensure that balanced vaccine safety information is communicated through media to prevent the public from biased information.
- Ensure the implementation of AEFI related recommendations/ decisions reaching up to the lower level.

6.1.2. EFDA

- Monitor and evaluate implementation of AEFI surveillance in collaboration with stakeholders.
- Design and adopt new AEFI monitoring initiatives.
- Revise, update, distribute and ensure availability of AEFI monitoring tools.
- Strengthen Pharmacovigilance Advisory Committee and provide secretariat service for causality assessment.
- Strengthen AEFI data management system at all levels.
- Share AEFI data to relevant stakeholders and global community.

- Provide and follow training of personnel involved in AEFI surveillance in collaboration with other stakeholders.
- Analyse AEFI data and providing feedback to stakeholders.
- Establish stakeholders' coordination platform.
- Carry out risk- benefit analysis of vaccine used in the immunization program.
- Take the necessary corrective measures when there is a safety and/or quality problem of vaccine is observed.
- Communicate AEFI and immunization safety that needs public attention at the national level with MOH.
- Establish /strengthen efficient communication mechanisms on vaccine safety among stakeholders.
- Support regions and strengthening AEFI documentation and reporting system.
- Engage in the planning, training, implementation and monitoring of related activities organized by MOH-EPI
- Collaborate with MOH-EPI mobilizing resources to strengthen AEFI monitoring.
- Engage in national immunization taskforce/TWG.
- Verify submission and review of risk management plans prior to market authorization and making recommendation for post authorization safety surveillance.
- Oversee the monitoring of vaccine safety by reviewing periodic safety update report (PSUR) and periodic benefit-risk evaluation report (PBRER)

The branch EFDA offices coordinate AEFI monitoring activities in collaboration with sub national stakeholders in their respective areas.

6.1.3. Ethiopian Public Health Institute (EPHI)

- Collaborate with EFDA during AEFI surveillance.
- Conduct laboratory analysis of specimens collected during AEFI investigation.
- Collaborate with EFDA during outbreak response vaccination campaign.
- Conduct epidemiological studies related to vaccine safety monitoring in collaboration with EFDA.
- Collaborate on post marketing clinical trials of vaccines.

6.1.4. Regional EPI and Regulatory bodies

In the AEFI monitoring system regional EPI and regulatory bodies are responsible for: -

- Monitoring of timely reporting of AEFI cases by health professionals
- Collaboration with EFDA branch offices on AEFI monitoring activities.
- Collaboration with EFDA on sharing of AEFI related information, training materials, relevant tools
- Provide AEFI monitoring trainings to health professionals.
- Handling and timely dissemination of well-organized information to community
- Coordinating and strengthening AEFI investigation taskforce
- Collaboration and facilitate AEFI case investigation to ensure timely completion of investigation.
- Conduct AEFI case investigations and share reports to EFDA for causality assessment.
- Strengthen AEFI data documentation and sharing.
- Ensure that AEFI kits are available at vaccination sites.
- Plan and evaluate performance of AEFI monitoring activities.
- Ensure that regulatory recommendations and decisions related to AEFI monitoring are implemented in their respective areas.

6.1.5. Woreda and Zonal EPI and regulatory bodies

In the AEFI monitoring system, Woreda and Zonal EPI and regulatory bodies are responsible for:

- Monitor and ensure AEFI detection, collection and reporting by health professionals.
- Collaborate with EFDA branch offices, regional EPI and regulatory bodies on AEFI monitoring activities.
- Collaborate with regional investigation taskforce during AEFI case investigation.
- Document AEFI data and share with the next higher level.
- Ensure the availability of AEFI kits at vaccination sites.
- Monitor and evaluate the performance of AEFI activities.
- Follow and ensure the implementation of regulatory recommendations and decisions.

- Ensure incorporation of AEFI activities in woreda based planning, micro plan and administrative planning.

6.1.6. EFDA Branch Offices

In the AEFI monitoring system EFDA branches are responsible for: -

- Monitoring of timely reporting of AEFI cases by health professionals
- Collaborate with EFDA on sharing of AEFI related information, training materials, relevant tools.
- Provide trainings to health professionals on AEFI monitoring.
- Handling and timely dissemination of well-organized information to community
- Coordinate and strengthen AEFI investigation taskforce.
- Collaborate and facilitate AEFI case investigation to ensure timely completion of investigation.
- Conduct AEFI case investigations and share reports to EFDA for causality assessment.
- Strengthen AEFI data documentation and sharing.
- Ensure availability of AEFI kit at vaccination sites
- Conduct planning and performance evaluation of AEFI monitoring actives.

6.1.7. Regional Pharmacovigilance Centres (RPVCs)

In the AEFI monitoring system RPVCs are responsible for: -

- Timely report AEFI cases in their hospitals
- Collaborate with EFDA branch offices on AEFI monitoring activities.
- Collaborate with EFDA on sharing of AEFI monitoring activities.
- Ensure organized AEFI data documentation.
- Ensure availability of AEFI kit at vaccination sites of hospital
- Closely work in hospitals service delivery points

6.1.8. National Pharmacovigilance Advisory Committee (NPAC)

The national pharmacovigilance advisory committee is composed of a multidisciplinary expert and with an independent decision-making power. It conducts causality assessment based on the available data and provide a recommendation to EFDA.

The NPAC is responsible for:

- Assess potential causal links between AEFIs and AESIs and vaccines.
- Monitor AEFI data for identification of potential signals of previously unidentified vaccine related adverse events.
- Review all serious AEFIs presented for expert opinion and arrange further investigation to establish causality, if required.
- Communicate with other national and international experts, when required, to establish causality and resolve vaccine quality issues.
- Advise NRAs, EPIs on vaccines AEFI- and AESI-related issues when requested.
- Advise the Ministry of Health (MoH) on vaccines and Immunization safety-related matters when requested.

6.1.9. The parent/guardian

Parents and guardians should follow health professionals' advice for:

- Applying simple home remedies (e.g. correct positioning of the child when sleeping, increasing intake of fluids, sponging, breast feeding, antipyretics etc.) for managing minor AEFIs
- Returning immediately to health care facilities if severe/serious AEFI occurs
- Notify health professionals of any AEFI encountered.

6.1.10. The health professionals

- Advise vaccine recipients or their parents/care givers about AEFI management and notification.
- Detection, management and recording of AEFIs.
- Notification and reporting of AEFIs using the standard reporting tools.
- Keep AEFI monitoring related documents properly such as AEFI line list, copy of reported serious AEFIs.
- Properly document patient medical chart after management of suspected AEFI
- Collaborate with AEFI case investigation taskforce during investigations.
- Implement feedback provided on AEFI monitoring from higher administrative level.

6.1.11. Developmental Partners

- Sharing of global good practices on AEFI monitoring
- Plan for AEFI monitoring activities in collaboration with the national PV centre.
- Provide technical and financial support for AEFI monitoring activities.
- Ensure appropriate mobilization of resources.

7. Safety Communication

Vaccine safety communication is crucial for the successful implementation of an immunization program and to maintain public trust and confidence in the vaccination programs. It is essential in at least three situations:

- Explaining properly the benefits and expected AEFIs of a recommended vaccine.
- Addressing public concerns and upcoming or persistent rumours about vaccine safety
- Preparing to address vaccine safety crises if and when they occur.

Communication with parents/guardians, the community, HCPs and the media need to be carried out under many circumstances, from launching new vaccines and putting in place mass immunization campaigns to issuing reminders to maintain vaccinations up to date. When a vaccine safety investigation is under way as a result of a report of an AEFI, communications involve keeping the public informed about the investigation, the results, and actions already taken or to be taken regarding the AEFI. At the same time, it is crucial to highlight the benefits of immunization even while communicating about an investigation.

The overall goal of vaccine safety communication is to maintain public trust in vaccines and immunization safety to sustain the immunization program and achieve a high level of immunization coverage. The specific objectives of vaccine safety communication are to:

- Enable parents/guardians and communities understand the importance of vaccines and immunization.
- Restore confidence in vaccines and express trust in the national immunization programme.
- Support parents/guardians complete their children's immunization schedules.
- Enable program managers, health professionals, the media and other stakeholders to deal with vaccine safety related rumours and misinformation.
- Enable the mass media and social media to disseminate accurate and evidence-based information about vaccine safety.
- Timely communicate AEFI causality assessment classification results

Identification of particular interest groups and their representatives should be part of an overall communication strategy. Decisions including what, when, whom and how to communicate should be part of an overall communication strategy. It is very important to understand the nature of an AEFI and

also whether it is real or perceived, because any AEFI can become a crisis situation if not handled correctly and wisely.

7.1. Vaccine safety communication during crisis

A crisis related to a vaccine is an unexpected series of events that may happen after a vaccine has been administered to a population group particularly during or at the end of a campaign. A crisis may arise when something goes wrong, for example as a result of genuine vaccine reactions or due to immunization-related errors that cause parents/guardians to withhold immunization of their children. A crisis may be caused by media publicity about an AEFI incident, even if it may have no basis or is triggered by unfounded rumours. The crisis may be made worse by a "cover-up" that is subsequently found out. This is why programme managers must act in a timely manner by mobilizing the communication task force, the technical group, spokespersons and media partners to dispel any misinformation quickly before it becomes a crisis.

Crisis communication is a combined effort by health and immunization programme managers, the regulatory authority and local leaders to address public concern about vaccine safety through appropriate channels. Messages should assure the public that a vaccine safety issue is being investigated and will be resolved, and that the immunization programme will continue.

7.2. Communication with stakeholders

There are many parties to whom communications should be tailored in order to meet their particular needs. These include:

- Parents/guardians and the community
- Health professionals
- Particular stakeholders such as the MOH, EPHI, EPSS, politicians, professional associations, academia, international agencies and development partners, such as WHO, UNICEF, Pharmacovigilance Advisory Committee, regional investigation task force, policy makers and other government authorities, health facilities, MAHs and
- The media

The following principles of communication apply to most of the stakeholders:

- Listen empathetically to concerns.
- Reassure and support but do not make false promises.
- Communicate frequently.
- Build up and maintain relationship among the stakeholders.

- Inform audiences about possible common adverse events and how to handle them.
- Prepare fact sheets on adverse events and other key information for all audiences.
- Continuously communicate during the investigation period in order to ensure understanding both of the situation and of the balance of risk and benefit of vaccination

Do not apportion blame, especially on the HCPs, but focus on the correction and quality of the national immunization programme.

7.2.1. Communication with clients, parents/guardians and the community

Key points to consider when communicating with the vaccine recipient (patient or client) or parents/guardians, and the community are:

- Listen to the clients', parents/guardians' and the community's concerns empathetically.
- Reassure and support the client and/or parent/guardian but do not make false promises.
- Prepare and provide a fact sheet on adverse event for the clients and/or parents/guardians and the community.
- Inform the individual client and/or parent/guardian about possible common adverse events and how to handle them.
- Continuously communicate with the client and/or parent/guardian and the community during the investigation

7.2.2. Role of health professionals in community communication on AEFI

Vaccinators at various levels need to be able to provide information to parents/guardians and handle queries from the community, especially from parents/guardians. Those who routinely administer vaccines, or who evaluate and treat patients, including medical officers, clinical officers and nurses, should receive training and regular updates on vaccine safety and quality issues, news and research. Health professionals and vaccinators should be trained about vaccine safety communication to share accurate immunization facts, respond to questions, clarify possible doubts, and motivate families to adopt healthy behavioural practices, including using immunization services.

Once an AEFI has occurred, HCPs should do the following:

- Communicate immediately with the immediate higher level in the EPI, regulatory and EFDA.
- Provide the parents with factual information.
- Reassure parents/guardians and the community that necessary measures are being taken.
- If the AEFI is caused by an immunization error, inform the parents/guardians and the community what steps are being taken to prevent similar events in the future.

- Reassure the public about the safety of vaccines.

7.2.3. Communication with health professionals

Because of the nature of their work, HCPs should have some training, or at least experience in communication skills. Communication with HCPs by EFDA and investigators should be sensitive to their needs. Therefore:

- Communication should include all levels of health authorities involved.
- Reassure the staff of their knowledge, ability, skills and performance.
- Do not blame HCPs but focus on the correction and quality of the national immunization programme.
- Keep HCPs updated on the investigation process, progress, and findings

7.2.4. Communicating with community and/or religious leaders

Community and/or religious leaders are regarded by their constituents as credible sources of information. They have the power to shape public opinions and can improve the links between families, communities and health services. Religious leaders can serve as effective communication channels and social mobilizers when it comes to combatting rumours and unfounded negative opinions about vaccine safety. The community and/or religious leaders should be informed about any upcoming major EPI event such as new vaccine introduction, mass campaign etc., so that they take the lead during communication and social mobilization. When there is a crisis, early communication with community and/or religious leaders is very important. An advocacy kit with briefing notes and scripted key messages, that they could use to communicate with their constituents, should be provided to them.

7.3. Communicating with the Media

The media is an important gateway to inform the public and shapes their view and attitudes towards vaccines and immunization, especially including the occasional vaccination campaigns. In the long-term, building partnerships with the media is key to keep the public regularly informed about immunization, its benefits and to motivate families and communities to make use of immunization services.

Effective communication with the media includes advance preparation. This is part of a communication plan and is particularly important before a new vaccine is introduced or before and during an immunization campaign. A communication plan can also provide ongoing communication support to routine immunization programmes. Table 17 lists the elements of a good media plan for communication.

Table 17: Media plan for communication.

Database of journalists	• Maintain a list of print and electronic media journalists covering health with contact information • Update regularly any changes in the media list
Information packages	• An information package may contain the following documents in both hard copy and e-copies: • Frequently asked questions (FAQs) on immunization in general and for AEFI • Fact sheet or a technical brief on a specific vaccine's safety background rates of AEFI and expected AEFI rates • Recent updates such as statistics, progress made in the country, globally • Contact addresses of spokespersons (experts) in the MOH, regulatory authorities and other stakeholders • The information package needs to be updated regularly.
Media releases	• Must specifically answer the 7 Ws for journalists: • 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?
Information specific to media characteristics	• Local media are read and believed by more people in the community than national media • National media have a wide reach and influence national agendas • International media can influence national agendas
Spokesperson system	The MOH and/or EFDA: • Identify an appropriate spokesperson(s)

	• May delegate this responsibility to RHBs if deemed necessary. • Share contact details of spokesperson. • Ensure spokesperson(s) has experience or training in dealing with the media

Note: The MOH and/or EFDA shall be responsible for communicating the AEFI to media, public and stakeholders to limit the possibility of conflicting messages coming from different sources and unauthorized channels.

Media interest is usually greatest initially when relatively little is known. In this environment, rumours can flourish and the potential for harm is huge. A media conference, convened early even if there is only very limited information to give, can provide a uniform message to all at the same time, thus avoiding conflicting messages. This will also prevent the circulation of rumours and build a relationship with reporters. Professional organizations and other stakeholders may have greater credibility than the government, particularly in a crisis situation. Providing them an opportunity for their unified support for immunization and the approach being taken to handle/investigate the problem can help considerably.

7.4. Follow-up actions with communications

Keeping promises: If it has been promised that updates about the investigation will be disseminated, make sure that this is done by the promised date. If the findings have been delayed, ensure that the delay is communicated.

Providing answers to unanswered questions: If a question cannot be answered for any reason, get back to the requestors with the answers as soon as possible.

Keeping the public informed about subsequent developments: If any decision or action is taken at the highest levels following the AEFI investigations, or during the investigations, and the public must know about it, keep them informed through a press release to the media or other locally appropriate means. The MOH website www.moh.gov.et and the EFDA website www.efda.gov.et can be used as an excellent interface to provide updated information.

8. Monitoring and Evaluation of AEFI Surveillance system

Monitoring and Evaluation (M&E) is very essential in the health system in general and in monitoring AEFI surveillance system. The overall AEFI surveillance system should be monitored and evaluated at all levels of surveillance cycle (Fig. 1). This system could be examined with usual M&E parameters: the input or resources used to conduct the activities or the processes for attaining the immediate result or output and medium-term results or outcome to the community, and ultimately the long-term impact to the entire population.

The overall goal of monitoring AEFI is early detection and timely response to AEFI, to minimize negative effects to the health of individuals and of population. In this connection, the effort or performance of AEFI surveillance system needs to be regularly measured at all levels using appropriate indicators to ensure that the system is sensitive enough to identify and respond to AEFI effectively.

8.1. Monitoring arrangements/ platforms

The following platforms will be used for monitoring of the AEFI activities.

Periodic Reports: weekly, monthly, quarterly and annually using selected AEFI indicators as appropriate.

Review Meeting: this could be arranged by Performance Monitoring Team (PMT) of respective structure of health facility, Woreda, Zone, RHB/RRB and national level, monthly, quarterly, biannual and annually depending on the context.

Supportive Supervision: is a process that individuals or groups of people from relevant stakeholders' conduct site visit to a specific facility to promote quality at all levels of the health system by strengthening relationships within the system, focusing on the identification and resolution of problems, and helping to optimize the allocation of resources, promotion of high standards, teamwork, and facilitation of two-way communications.

Supportive supervision at all levels should be conducted based on a predefined checklist developed to assess the progress of key aspects of AEFI monitoring. EFDA or its branch, RHB, WoHOs, ZHDs, and health facility management should have clearly defined objectives and a timeline to provide regular supportive supervision. The onsite supportive supervision for AEFI monitoring can be carried out independently or integrated with other EPI activities. The frequency of supportive supervision at sub national level will be at least on quarterly basis under regular condition within appropriate time while at the national level it will be carried out at least biannually.

Depending on the context, additional monitoring platforms such as during campaigns and other special conditions could be considered. Continuous monitoring and periodic evaluation of AEFI using quality data enable us to measure and improve performance and to make decisions in a timely manner. The parameters could be extracted from the logical process as inputs indicators; availability of plan, resources, tools and materials, while for the process indicators include the activities conducted to achieve the desired output.

A similar approach could be used to have indicators for measuring the outcome and impact parameters. The indicators are expected to give a panoramic view of the AEFI landscape and criteria to select appropriate indicators are practicality/ accessible and feasible, pertinent/relevant, simple (in terms of time, money and complexity), sensitive, specific, verifiable, technically valid/ importance of the information. These context-based criteria and standard references could be used to select the measurement indicators. Furthermore, a few of these will be considered in the DHIS2 tracking system.

8.2. AEFI monitoring Indicators.

a) Input Indicators

- Availability of AEFI tools (recording and reporting forms)
- Availability of AEFI job aids (guideline, SOPs)
- Availability of plan for AEFI monitoring
- Availability of budget for AEFI monitoring
- Availability of assigned focal person in health facilities for AEFI monitoring.
- Availability of functional regional investigation taskforce
- Availability of functional National Pharmacovigilance Advisory Committee

b) Process and outputs indicators.

- Number of professionals trained on AEFI monitoring/ PV in the past 2 years.
- Number of AEFIs detected from the number of vaccinations provided.
- AEFI reporting rate per 100 000 population.
- AEFI reporting rate per 100 000 < 5 years population.
- AEFI reporting rate per 1 000 000 administered doses of vaccines.
- AEFI reporting ratio in surviving infants from a sub-national area or country per year.

This is calculated as: AEFI reporting ratio per 100,000 surviving infants per year.

$$= \frac{\text{Number of AEFI cases reported from a subnational area/country per year}}{\text{Total number of surviving infants in the same subnational area/country per year}} x\ 100{,}000$$

- % of AEFI reports with completed critical information (completeness of reports)
- Percentage of SAEs reported on time (< 24 hours of notification) to the national level.
- Percentage of serious AEFI cases for which investigation is initiated on time (within 15 days of receipt of report).
- Percentage of ICSR entered into the vigiflow.
- Percentage of ICSR on vigiflow shared to the global database.
- Functionality of regional investigational task force
- Proportion of causality assessment conducted from investigated AEs
- Proportion of causality assessment completed within 30 days of receipt of investigation report.
- Proportion of feedback/ responses provided for SAEs (excluding acknowledgement letter)
- Number of regulatory decisions (recommendation, action) taken in the reporting period.

Table 18: Brief description on M&E Key Performance Indicators for AEFI

SN	Indicator	Type of Indicator	Level of Data Collection	Data Source	Frequency of data collection/ Analysis	Baseline	Target
1.	Availability of AEFI monitoring plan	Input	All levels	Document Review	Quarterly		
2.	Functionality of Regional TF	Output	RHB	Records	Annually		
3.	AEFI reporting ratio in surviving infants	Output	All levels	Reg book	Monthly		
4.	Proportion of causality assessment conducted from investigated SAEs	Output		Records	Annually		
5.	Proportion of feedback/ responses provided for SAEs (excluding	Output	National	Records	Annually		

	acknowledgement letter)						

9. References

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13. National Implementation Guideline for Expanded Program on Immunization. Addis Ababa: Ministry of Health, 2021.
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10. Annexes

Annex I: AEFI Reporting Form

Ethiopian Food and Drug Authority (EFDA)

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

*Patient Name or initials:_____	*Reporter's Name : _____
*Patient's full Address:_____	Institution :_____
Telephone : _____	Profession : _____
Sex : M ☐ F ☐ Pregnant ☐ Lactating ☐	Title & Department :_____
*Date of birth :__ __/__ __/__ __ __ __	Telephone :_____
Or Age at onset: __ __ years __ __ months __ __ __ days	Email :_____
Or Age group at onset: < 1 year☐ 1 to 5 yrs☐ 6 to 15 yrs☐	Date patient notified event to health system : __/__/__
16 to 60 yrs☐ >60 yrs☐	Today's date:__ __ / __ __/____

Health facility or vaccination center name & address:						
Vaccine						
Name of vaccine	*Brand Name and, Name of Manufacturer	*Date of vaccination	*Time of vaccination	Dose (1st, 2nd, Booster etc.)	*Batch /Lot number	Expiry date
Diluents *(if applicable)*						
Name of diluent	*Batch /Lot number	Expiry date	Date of reconstitution		Time of reconstitution	

* Mandatory

***Adverse event(s):** ☐ Severe local reaction ☐ >3 days ☐ beyond nearest joint ☐ Seizures ☐ afebrile ☐ febrile ☐ Abscess ☐ Sepsis ☐ Encephalopathy ☐ Toxic shock syndrome ☐ Thrombocytopenia ☐ Anaphylaxis ☐ Fever ≥38°C ☐ Redness/tenderness/itching at injection site ☐ Generalized itch ☐ Rash ☐ Thrombosis (Pulmonary Embolism and Deep Vein Thrombosis) ☐ Other (specify).....	Date AEFI started: __ / __ / __ Time AEFI started: _____ Resolved date (leave blank if ongoing): __ / __ / __ Resolved time (leave blank if ongoing): _____ Describe AEFI (Signs and Symptoms): _____ _____ _____ _____ _____

Serious: Yes/No; If Yes Death ☐ Life threatening ☐ Persistent or significant disability ☐ Hospitalization ☐ Congenital anomaly ☐ Other important medical event ☐ (Specify).....
Outcome: Recovering ☐ Recovered ☐ Recovered with sequela ☐ Not Recovered ☐ Unknown ☐ Died ☐ If died, date of death: _ _ / _ _ / _ _ Autopsy done: Yes ☐ No ☐ Unknown ☐
Past medical history (including history of similar reaction or other allergies), concomitant medication and dates of administration (exclude those used to treat reaction) other relevant information (e.g., other cases). use additional sheet if needed

First decision making level to complete: (eq.Woreda Health Office)

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

National level to complete: (EFDA)

Date report received at national level _ _ / _ _ / _ _	AEFI worldwide unique ID:
Comments:	

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This AEFI reporting form is prepared and printed by the Ethiopian Food and Drug Authority (EFDA) in collaboration with the Global Health Supply Chain Program- Procurement and Supply Management (GHSC-PSM) project with a financial support from USAID.

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From ----------

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ETHIOPIAN FOOD AND DRUG AUTHORITY

Other means of Reporting
Electronic Reporting form on our website: www.efda.gov.et
Med safety Mobile application download from play store or IOM
Email address: pharmacovigilance@efda.gov.et
Toll free telephone: 8482

P.O. Box 5681-Tel.0115-523142
Addis Ababa, Ethiopia

Annex II: AEFI Investigation Form

Dec 2023

ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI) INVESTIGATION FORM

(Only for Serious Adverse Events Following Immunization: Death / Disability / Hospitalization / Cluster)

Section A — Basic details

Province/State District Case ID

Place of vaccination (✓): ☐ Govt. health facility ☐ Private health facility ☐ Other (specify) _____
Vaccination in (✓): ☐ Campaign ☐ Routine ☐ Other (specify) _____

Address of vaccination site:

Name of Reporting Officer:

Date of investigation:_____/_____/_____
Date of filling this form:_____/_____/_____

Designation / Position:

This report is: ☐ *First* ☐ *Interim* ☐ *Final*

Telephone # landline (with code): Mobile: e-mail:

Patient Name Sex: ☐ M ☐ F

(use a separate form for each case in a cluster)

Date of birth (DD/MM/YYYY):_____/_____/_____

OR Age at onset:_____years_____months_____days

OR Age group: ☐ *< 1 year* ☐ *1–5 years* ☐ *> 5 years - 18 years* ☐ *> 18 years – 60 years* ☐ *> 60 years*

Patient's full address with landmarks *(Street name, house number, locality, phone number etc.)*:

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

Type of site (✓) ☐ Fixed ☐ Mobile ☐ Outreach ☐ Other _____

Date of first/key symptom *(DD/MM/YYYY)*:_____/_____/_____ Time of first symptom *(hh/mm)*:_____/_____
Date of hospitalization *(DD/MM/YYYY)*: _____/_____/_____
Date first reported to the health authority *(DD/MM/YYYY)*:_____/_____/_____

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

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

Section B — Relevant patient information prior to immunization

Criteria	Finding	Remarks (If yes provide details)
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	
History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women • Currently pregnant? Yes (weeks)_____/ No / Unknown • Currently breastfeeding? Yes / No		

For infants

The birth was ☐ full-term ☐ pre-term ☐ post-term. Birth weight:

Delivery procedure was ☐ Normal ☐ Caesarean ☐ Assisted (forceps, vacuum etc.) ☐ with complication (specify)

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

Source of information (✓ *all that apply*): ☐ **Examination by the investigator** ☐ **Documents** ☐ **Verbal autopsy**
☐ **Other**_____ *If from verbal autopsy, please mention source* _____

Name of the person who first examined/treated the patient:_____
Name of other persons treating the patient: _____
Other sources who provided information (specify): _____

Signs and symptoms in chronological order from the time of vaccination:

Name and contact information of person completing these clinical details:	Designation:	Date/time

Instructions – Attach copies of ALL available documents (including case sheet, discharge summary, case notes, laboratory reports and autopsy reports, prescriptions for concomitant medication) and then complete additional information NOT AVAILABLE in existing documents, i.e.

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

Provisional / Final diagnosis:

Section D Details of vaccines provided at the site linked to AEFI on the corresponding day

Number immunized for each antigen at session site. Attach record if available.	Vaccine name									
	Number of doses									

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

**It is compulsory for you to provide explanations for these answers separately*

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

(Complete this section by asking and/or observing practice)

Syringes and needles used:

• Are AD syringes used for immunization?	Yes / No / Unkn

If no, specify the type of syringes used: ☐ Glass ☐ Disposable ☐ Recycled Disposable ☐ Other _____

Specific key findings/additional observations and comments:

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

	Status		
• Reconstitution procedure (✓)			
Same reconstitution syringe used for multiple vials of same vaccine?	Yes	No	NA
Same reconstitution syringe used for reconstituting different vaccines?	Yes	No	NA
Separate reconstitution syringe for each vaccine vial?	Yes	No	NA
Separate reconstitution syringe for each vaccination?	Yes	No	NA
• Are the vaccines and diluents used the same as those recommended by the manufacturer?	Yes	No	NA

Specific key findings/additional observations and comments:

Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)

• Correct dose and route?	Yes / No
• Time of reconstitution mentioned on the vial? (in case of freeze-dried vaccines)	Yes / No
• Non-touch technique followed?	Yes / No

• Contraindications screened prior to vaccination?	Yes / No
• How many AEFI were reported from the Centre that distributed the vaccine in the last 30 days?	
• Training received by the vaccinator? (If yes, specify the date of last training_____)	Yes / No
Specific key findings/ additional observations and comments?	

Section F	**Cold chain and transport** *(Complete this section by asking and/or observing practice)*
Last vaccine storage point:	
• Is the temperature of the vaccine storage refrigerator monitored?	Yes / No
○ If "yes", was there any deviation outside of 2–8° C after the vaccine was placed inside?	Yes / No
○ If "yes", provide details of monitoring separately.	
• Was the correct procedure for storing vaccines, diluents and syringes followed?	Yes / No / Unkn
• Was any other item (other than EPI vaccines and diluents) in the refrigerator or freezer?	Yes / No / Unkn
• Were any partially used reconstituted vaccines in the refrigerator?	Yes / No / Unkn
• Were any unusable vaccines (expired, no label, VVM at stages 3 or 4, frozen) in the refrigerator?	Yes / No / Unkn
• Were any unusable diluents (expired, manufacturer not matched, cracked, dirty ampoule) in the store?	Yes / No / Unkn
Specific key findings/additional observations and comments:	
Vaccine transportation:	
• Type of vaccine carrier used	
• Was the vaccine carrier sent to the site on the same day as vaccination?	Yes / No / Unkn
• Was the vaccine carrier returned from the site on the same day as vaccination?	Yes / No / Unkn
• Was a conditioned ice-pack used?	Yes / No / Unkn
Specific key findings/additional observations and comments:	

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

Were any similar events reported within a time period similar to when the adverse event occurred and in the same locality?
Yes / No / Unknown If yes, describe:

If yes, how many events/episodes?

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

Other comments:

Section H Other findings/observations/comments

Annex III: The causality assessment checklist.

	Y	NU	K	NA	Remarks
I. Is their strong evidence for other causes?					
1. In this patient, does the medical history, clinical examination and/or investigations, confirm anothercause 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 eventif administered correctly?	□	□	□	□	
2. Is there a biological plausibility that this vaccinecould cause such an event?	□	□	□	□	
3. In this patient, did a specific test demonstrate thecausal role of the vaccine?	□	□	□	□	
Vaccine quality					
4. Could the vaccine given to this patient have a qualitydefect 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 thevaccine (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. color, 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.)?	□ □□ □	

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

	Y	NU K	N A	Remarks
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 vaccineand 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 conditionor 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.)?	□ □□ □	

Annex IV: Examples of AEFI case definitions*

AEFI	Case definition	Vaccine
Anaphylaxis	A clinical syndrome characterized by sudden onset (within one hour), rapid progression of signs and symptoms involving multiple (more than two) organ systems: **Skin:** urticaria (hives), angioedema (swelling of face/body), generalized erythema, bilateral red and itchy eyes of new onset **Respiratory**: expiratory wheeze and inspiratory stridor documented by a healthcare professional, cough and/or sneezing and/or runny nose that is new onset and persistent, respiratory distress (tachypnoea, cyanosis, grunting, chest wall retractions, increased use of accessory respiratory muscles and measured hypoxia with oxygen saturation <90%.) **Cardiovascular:** low blood pressure (hypotension) or reduced circulation (fast weak pulses), loss of consciousness **Gastrointestinal:** new onset vomiting and diarrhea (for infants <12 months old, there must be two or more episodes)	All
BCG osteitis/ osteomyelitis	Inflammation of the bone with isolation of *Mycobacterium bovis* BCG strain.	BCG
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of Mycobacterium bovis BCG strain. Usually in immuno-compromised individuals.	BCG
Encephalopathy	Abnormal level of alertness /consciousness or seizures, difficulty with initiating and maintaining respiration, depression of tone	Measles, Pertussis

AEFI	Case definition	Vaccine
Fever	Endogenous elevation of at least one measured body temperature of ≥38 °C	All
Hypotonic, Hyporesponsive Episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 (usually less than 12) hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • limpness (hypotonic) • reduced responsiveness (hypo responsive) or unresponsiveness • pallor or cyanosis – or failure to observe/ recall.	Mainly DPT, rarely others
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, positive bacterial culture), Sterile abscess if no evidence of bacterial infection on culture. Erythema, pain to light touch, warmth at the injection site sterile abscesses is usually due to the inherent properties of the vaccine.	All injectable vaccines
Intussusception	**10.1.1.1.** Major criteria • *Surgical criteria*: The demonstration of invagination of the intestine at surgery. o *and*/*or* • *Radiologic criteria*: The demonstration of invagination of the intestine by either air or liquid contrast enema; *or* The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic	Rotavirus

AEFI	Case definition	Vaccine
	features[2] that is proven to be *reduced* by hydrostatic enema on *post reduction ultrasound*; o *and/or* • *Autopsy criteria*: The demonstration of invagination of the intestine. **10.1.1.2.** Minor criteria o Predisposing factors: age <1 year and male sex. o Abdominal pain o Vomiting o Lethargy o Pallor o Hypovolemic shock. o Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern. IS occurring within 42 days following immunization.	
Lymphadenitis (includes suppurative lymphadenitis)	Either at least one lymph node enlarged to >1.5 cm in size (one adult finger width) or a draining sinus over a lymph node. Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary).	BCG
Persistent inconsolable screaming	Inconsolable and continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	DPT, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >100.4 ^{0}F or 38 ^{0}C (rectal)	All, especially Pertussis, Measles

AEFI	Case definition	Vaccine
	Afebrile seizures: if temperature is normal	
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture.	All injectable vaccines
Severe local reaction	Redness and/or swelling cantered 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 and interfering with daily activities. • Requires hospitalization. Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.	All injectable vaccines
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours.	All injectable vaccines
Vaccine Associated Paralytic Poliomyelitis (presenting as AFP)	Acute onset of flaccid paralysis and neurological deficits, compatible with diagnosis of poliomyelitis, with isolation of vaccine virus and absence of wild virus in stool.	OPV

AEFI	Case definition	Vaccine
Anaphylaxis	A clinical syndrome characterized by sudden onset (within one hour), rapid progression of signs and symptoms involving multiple (more than two) organ systems: **Skin:** urticaria (hives), angioedema (swelling of face/body), generalized erythema, bilateral red and itchy eyes of new onset	All

AEFI	Case definition	Vaccine
	Respiratory: expiratory wheeze and inspiratory stridor documented by a healthcare professional, cough and/or sneezing and/or runny nose that is new onset and persistent, respiratory distress (tachypnoea, cyanosis, grunting, chest wall retractions, increased use of accessory respiratory muscles and measured hypoxia with oxygen saturation <90%.) **Cardiovascular:** low blood pressure (hypotension) or reduced circulation (fast weak pulses), loss of consciousness **Gastrointestinal:** new onset vomiting and diarrhea (for infants <12 months old, there must be two or more episodes)	
BCG osteitis/ osteomyelitis	Inflammation of the bone with isolation of *Mycobacterium bovis* BCG strain.	BCG
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination and confirmed by isolation of Mycobacterium bovis BCG strain. Usually in immuno-compromised individuals.	BCG
Encephalopathy	Abnormal level of alertness /consciousness or seizures, difficulty with initiating and maintaining respiration, depression of tone	Measles, Pertussis
Fever	Endogenous elevation of at least one measured body temperature of ≥38 °C	All
Hypotonic, Hyporesponsive Episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 (usually less than 12) hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • limpness (hypotonic) • reduced responsiveness (hypo responsive) or unresponsiveness • pallor or cyanosis – or failure to observe/ recall.	Mainly DPT, rarely others

AEFI	Case definition	Vaccine
Injection site abscess	Fluctuant or draining fluid-filled lesion at the site of injection. Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, positive bacterial culture), Sterile abscess if no evidence of bacterial infection on culture. Erythema, pain to light touch, warmth at the injection site sterile abscesses is usually due to the inherent properties of the vaccine.	All injectable vaccines
Intussusception	**10.1.1.3.** Major criteria • *Surgical criteria*: The demonstration of invagination of the intestine at surgery. o *and/or* • *Radiologic criteria*: The demonstration of invagination of the intestine by either air or liquid contrast enema; *or* The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features[2] that is proven to be *reduced* by hydrostatic enema on *post reduction ultrasound*; o *and/or* • *Autopsy criteria*: The demonstration of invagination of the intestine. **10.1.1.4.** Minor criteria o Predisposing factors: age <1 year and male sex. o Abdominal pain o Vomiting o Lethargy o Pallor	Rotavirus

AEFI	Case definition	Vaccine
	○ Hypovolemic shock. ○ Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern. IS occurring within 42 days following immunization.	
Lymphadenitis (includes suppurative lymphadenitis)	Either at least one lymph node enlarged to >1.5 cm in size (one adult finger width) or a draining sinus over a lymph node. Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary).	BCG
Persistent inconsolable screaming	Inconsolable and continuous crying lasting 3 hours or longer accompanied by high-pitched screaming.	DPT, Pertussis
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >100.4 ^{0}F or 38 ^{0}C (rectal) Afebrile seizures: if temperature is normal	All, especially Pertussis, Measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture.	All injectable vaccines
Severe local reaction	Redness and/or swelling centered at the site of injection and one or more of the following: • Swelling beyond the nearest joint • Pain, redness and swelling of more than 3 days and interfering with daily activities. • Requires hospitalization. Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported.	All injectable vaccines

AEFI	Case definition	Vaccine
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours.	All injectable vaccines
Vaccine Associated Paralytic Poliomyelitis (presenting as AFP)	Acute onset of flaccid paralysis and neurological deficits, compatible with diagnosis of poliomyelitis, with isolation of vaccine virus and absence of wild virus in stool.	OPV

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

Annex V: AEFI Line List Format

AEFI line listing form for compilation at woredas or zonal/regional and national level to identify trends and clusters of AEFI.

Year: _____: _____

Name/ID of an AEFI	Kebele (write name	Woreda (write name	Zone (write name	Region	Date of birth	Date of immunisation	Reaction type (code)	Outcome (1)	Suspected vaccine	Vaccine batch/Lot	Diluent batch number	Onset time interval	Date reporting	Investigated? (If yes,	Final diagnosis	Result of causality

(Write code)

Final Causality Classification

[A1] Vaccine-related	[A2] Immunization error-related	[A3] Immunization anxiety-related	[B] Indeterminate	[C] Coincidental	[D] Inadequate information to classify

Reported by: _____ **Signature: _____**

Designation: _____ **Date: _____**