Ethiopian Food, Medicine and Healthcare Administration and Control Authority

Guideline for Surveillance and Response to Adverse Events Following Immunization

Third Edition

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Foreword

Vaccines are largely used to protect individuals particularly children from acquiring deadly infectious diseases which are preventable. Such products are relatively safe but can rarely cause adverse events following immunization (AEFI). A proportion of these may occur during immunization campaigns when vaccinating large populations in a short period or when new vaccines are introduced. As these serious adverse events are very rare and occur primarily in children who were apparently healthy, monitoring vaccine safety is of paramount importance in a healthcare system of any country.

AEFI surveillance system focuses on vaccine safety and it utilizes tools such as guidelines and procedures geared to assure public health protection through the use of vaccines with proven safety profile. The current system for monitoring drug safety (pharmacovigilance) is being coordinated by the National Regulatory Authority (NRA) called Ethiopian Food, Medicine and Healthcare Administration and Control Authority(EFMHACA). EFMHACA 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.

Monitoring vaccine safety has been challenging as there exist two safety data system in the country. The national expanded program on immunization (EPI), which has been actively engaged in enhancing immunization coverage, is also primarily collecting vaccine safety data from the woredas and AEFI reports which reach EPIdid not find their way to EFMHACA for further regulatory actions. The EPIat Federal Ministry of Health (FMoH) and EFMHACA have recently agreed to establish a coordinated mechanism for sharing vaccine safety data.

An effective and well-functioning AEFI surveillance system will eventually boost trust, public confidence and will also help improve the quality of the immunization program in the long run. It is therefore essential that all stakeholders like EPI, EFMHACA, vaccine manufacturers, laboratories, healthcare providers and development partners make concerted efforts to provide documented evidence 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 document will guide stakeholders at all levels to be involved in the strengthening of the AEFI surveillance system in Ethiopia.

It gives me a great pleasure to present this 3rdedition of Guideline for Surveillance and Response to Adverse Events Following Immunization for all those involved which will be kept under review asnecessary. I hope everyone will use this guideline effectively as a guide towards maintaining vaccinesafety and ultimately improve the safety and quality of healthcare being provided.

Finally, I would like to take this opportunity to thank all those who contributed in revising and printing this Guideline. I also call upon interested parties to continue their usual support by forwarding their comments and suggestions to the Ethiopian Food, Medicine and Healthcare Administration and Control Authority (EFMHACA), P.O.Box 5681 Addis Ababa, Ethiopia, Tel.251-115524122, e-mail regulatory@fmhaca.gov.et.

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Glossary

Adverse event following immunization (AEFI)	Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
Causal association	A cause-and-effect relationship between a causative (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 that is 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.
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 that is 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.
Immunization safety Surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
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).
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.
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 vaccine reaction	It refers to the intensity of vaccine reactions. A severe reaction refers to the high grade intensity of its grading such as mild moderate and severe. Severe reactions may include both serious and non-serious reactions.
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, that is judged to be of sufficient likelihood to justify verificatory action.

Surveillance	The continuing, systematic collection of data that will beanalyzed and disseminated to enable decision-making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
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 product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
Vaccine quality defect related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer
Vaccination failure	Vaccination failure may be defined on the basis of clinical endpoints or immunological criteria where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason or (ii) because the vaccine did not produce its intended effect
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.

Acronyms

ADRs	-	Adverse Drug Reactions
AEFI	-	Adverse Events Following Immunization
BCG	-	Bacillus Calmette-Guerin
CSF	-	Cerebrospinal fluid
WEO	-	WoredaEPI Officer
DT	-	Diphtheria Tetanus
DTaP	-	Diphtheria Tetanus Acellular Pertussis vaccine
DTwP	-	Diphtheria Tetanus Whole Cell Pertussis vaccine
DTPa-HepB-Hib	-	Diphtheria Tetanus Acellular Pertussis, Hepatitis B and Haemophilus influenza vaccine
EFMHACA	-	Ethiopian Food, Medicine and Healthcare Administration and Control Authority
EPHI	-	Ethiopian Public Health Institute
EPI	-	Expanded Program on Immunization
GVAP	-	Global Vaccine Action Plan
Hep B	-	Hepatitis B Vaccine
Hib	-	Haemophilus influenza type b vaccine
HHE	-	Hypotonic Hyporesponsive Episodes
IPV	-	Inactivated Polio Vaccine
LAV	-	Live Attenuated Vaccine
LP	-	Lumbar Puncture
EPI	-	National Immunization Program
NRA	-	National Regulatory Authority
OPV	-	Oral Polio Vaccine
MMR	-	Measles Mumps Rubella
MoH	-	Ministry of Health
NITAG	-	National Immunization Technical Advisory Group
OPV	-	Oral Polio Vaccine
PHEM	-	Public Health Emergency Management
PFSA	-	Pharmaceutical Fund and Supply Agency
PVV	-	Pentavalent Vaccine
REO	-	RegionalEPIOfficer
RHB	-	Regional Health Bureau
VAPP	-	Vaccine Associated Paralytic Poliomyelitis
VPD	-	Vaccine Preventable Disease
WHO	-	World Health Organization

1. Introduction

Vaccines are biological substances that are administered to individuals to elicit immunity (protection) against specific diseases. Such products are formulated together with adjuvants and/or excipients, and like all medical products, may cause adverse events following their administration to some individuals. Despite the fact that such adverse events following immunization (AEFIs) are mostly mild and very rarely severe, measures still need to be put in place to monitor and prevent their occurrence and take appropriate regulatory action(s) on the products themselves if needed.

A good vaccine is one that provides the best protection and gives rise to minimum adverse events. AEFIs can arise through a variety of reasons: these include events that could be inherent to the vaccine product, or related to the quality, or immunization error or immunization anxiety or could be coincidental. A robust AEFI surveillance system in a country will help authorities to detect, manage and prevent AEFIs.

In Ethiopia, the Federal Ministry of Health (FMoH) operates the Expanded Program on Immunization (EPI) through the National EPI Team. EPI is responsible for setting up policy guidelines for selection, supply and utilization of vaccines in the country. EPI has done a tremendous job and some of the notable achievements of the program include achieving immunization coverage of over 90 % for all primary immunization, establishing a cold chain system, engaging regional, zonaland woreda authorities in monitoring vaccine use, training and developing healthcare providers as well as establishing linkages and networking with international stakeholders.

Likewise, Ethiopian Food, Medicine and Healthcare Administration and Control Authority–(EFMHACA) has the mandate to monitor the safety of all medical products including vaccines. EFMHACA uses its pharmacovigilance system to collect any suspected adverse drug reactions experienced by patients. Itis also responsible for authorization of marketing all medicines including vaccines. All vaccine manufacturers are required by law to register their products before supplying and distributing them in the country.

Reporting of AEFI and subsequent investigation may trigger regulatory action including revoking the marketing authorization of a vaccine, instructing vaccine manufacturers to change their product labels, restricting the use of vaccines to specific client groups or recalling defective vaccine batches from the market.

The overall goal of immunization program/vaccination is the protection of the health and wellbeing of the entire population particularly infants, children and pregnant women and the general population who depend on vaccines to protect them from vaccine preventable diseases (VPD). This guideline outlines the processes and procedures to be followed by healthcare providers in reporting, documenting and preventing AEFIs, as well as the roles and responsibilities of stakeholders responsible for the planning and delivery of immunization programs in Ethiopia in close partnership. The guideline also outlines the surveillance system and provides tools and procedures needed to report and manage AEFIs. An understanding of the types of AEFIs, investigation techniques, specimen collection, managing AEFIs and communication including communicating with the media, are also described in this document.

It is anticipated that healthcare providers and EPI managers at different levels will read and use this guideline and thus appropriately manage, report, and prevent AEFIs in the country. The

guideline will also bring together stakeholders and allow for networking and improved collaboration in the process of detecting, analyzing and preventing AEFIs.

A brief introduction to causality assessment has been provided in this guideline. Advanced readers are encouraged to access the WHO website http://www.who.int/vaccine_safety/publications/gvs_aefi/en/ for more information.

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 VPD 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.

2.1.1. Primary components of vaccines

Vaccines may be monovalent or multivalent (polyvalent). A monovalent vaccine contains a single strain of a single antigen/immunogen (e.g. measles vaccine), whereas a polyvalent vaccine contains two or more strains/serotypes of the same antigen/immunogen (e.g. t OPV and IPV each of which contain three attenuated polio virus types).

Combination (or combined) vaccines contain two or more different antigens (e.g. DTwP, DTPa-HepB-Hib). The potential advantages of combination vaccines include reduction in the cost and difficulty of shipping and storing and administering multiple vaccines, avoiding multiple injections, reducing the cost of extra health-care visits, improving timeliness of vaccination, and facilitating the addition of new vaccines into immunization programs.

There is no evidence that the administration of several antigens in combined vaccines increases the burden on the immune system, which is capable of responding to millions of antigens at a time. Combining antigens usually does not increase the risk of adverse reactions and can lead to an overall reduction in adverse reactions. For instance, it can decrease the number of anxiety-related reactions and the chances of immunization error-related reactions.

2.1.2. Other components of vaccines

In addition to the primary antigen(s), vaccines contain small quantities of other substances. Sometimes AEFI can result from one of the other substances. They include,

Adjuvants: Sometimes a substance is added to a vaccine to enhance the immune response by degree and/or duration, making it possible to reduce the amount of immunogenic per dose or the total number of doses needed to achieve immunity. The commonly used adjuvants are aluminum salts (aluminum hydroxide, aluminum phosphate or potassium aluminum sulfate) 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 abscess, granulomatous inflammation or contact hypersensitivity.

Antibiotics: 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 contains less than 25 micrograms of neomycin per dose (less than 0.000025g). Recipients who are known to be allergic to neomycin should not be vaccinated and be closely observed if vaccinated unknowingly so that any allergic reaction can be treated immediately.

Preservatives: These 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 multidose vials as a result of bacterial or fungal contamination after they are opened.

*Stabilizers:*To confirm product quality or stability, compounds may be added to vaccines for a variety of manufacture related issues: controlling acidity (pH); stabilizing antigensthrough 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. Classification of vaccines

There are four types of vaccines: live attenuated, inactivated (killed antigen), subunit (purified antigen) and toxoids (inactivated toxic compounds). The characteristics of these vaccines differ, and the characteristics determine how the vaccine works.

Live Attenuated Vaccine (LAV)

LAV is derived from "wild," or disease-causing, virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. The resulting vaccine organism retains the ability to replicate (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 LAV, the first dose usually provides protection. An additional dose is given to ensure sero-conversion. For instance, 95% to 98% of recipients will respond to a single dose of measles vaccine. The second dose is given to assure that nearly 100% of persons are immune (i.e. the second dose is "insurance"). Immunity following live vaccines is long-lasting, and booster doses are not necessary, with the exception of oral polio vaccine, which requires multiple doses. LAV is labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully. Currently available LAV includes measles, mumps, rubella, varicella, yellow fever, oral polio and influenza (intranasal). Live-attenuated bacterial vaccines include BCG and oral typhoid vaccine.

Inactivated whole-cell vaccines

Inactivated vaccines are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals (usually formalin). Because they are not alive, they cannot grow in a vaccinated individual and, therefore, cannot cause the disease, even in an immunodeficient person. 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 antibody. They are often more stable than LAV.

Growing whole bacteria (e.g. whole-cell pertussis vaccine) or viruses (e.g. inactivated Poliomyelitis vaccine) in culture media, then treating them with heat and/or chemicals, produces an inactivated, non-viable vaccine. 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 humeral and little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

Subunit vaccines

The whole organism is grown in culture media and then the organism is further treated to purify only those components to be included in the vaccine (e.g. acellular pertussis and the meningococcal B vaccine).

Protein-based

Subunit vaccines can be protein-based. For example, the hepatitis B vaccine is made by inserting a segment of the hepatitis B virus gene into a yeast cell. The modified yeast cell produces large amounts of hepatitis B surface antigen, which is purified and harvested and used to produce the vaccine. The recombinant hepatitis B vaccine is identical to the natural hepatitis B surface antigen, but does not contain virus DNA and is unable to produce infection. Another protein-based vaccine is cellular pertussis (aP) vaccine which contains inactivated pertussis toxin (protein).

Polysaccharide vaccines

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

Conjugated vaccines

Children under two years of age do not respond well to antigens, such as polysaccharides, which produce antibodies via a T-cell independent mechanism. If these polysaccharide antigens are chemically linked (conjugated) to a protein that T-cells recognize, then these conjugate vaccines can elicit strong immune responses and immune memory in young children.

Toxoid Vaccines

In some bacterial infections (e.g. diphtheria, tetanus), the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by purifying the toxin and altering it chemically (usually with formaldehyde). While no longer toxic, the toxoid is still capable of inducing a specific immune response protective against the effects of the toxin.

Table 2.1. Classification of vaccines

Live attenuated vaccines(LAV)	**Bacteria:** BCG vaccine
	Virus: oral poliovirus vaccine, measles vaccine, mumps vaccine, rotavirus vaccine, rubella vaccine, yellow fever vaccine
Inactivated (killed antigen) vaccines	**Bacteria:** Whole -cell pertussis (wP)
	Virus: inactivated poliovirus vaccine (IPV)
Subunit vaccines (purified antigens)	**Protein-based:** Hepatitis B vaccine Acellular pertussis vaccine(aP)
	Polysaccharide: Meningococcal polysaccharide vaccine Pneumococcal polysaccharide vaccine
	Conjugate vaccine: Haemophilus influenzae type b (Hib) conjugate vaccine, meningitis A and B conjugate vaccine Pneumococcal conjugate vaccines (PCV-7, PCV-10, PCV-13) Vi conjugate vaccine
Toxoids	Tetanus toxoid Diphtheria toxoid

2.1.4. Contraindications and precautions to vaccination

A contraindication to vaccination is a rare characteristic 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 would-be recipient is immunocompromised or pregnant). Precautions stated in the product labeling may sometimes be inappropriately interpreted as contraindications, resulting in missed opportunities to vaccinate.

2.2. Adverse Events Following Immunization (AEFI)

An adverse event following immunization is any untoward medical occurrence (unfavorable or unintended sign, abnormal laboratory finding, symptom or disease) which follows immunization and which 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 Council for International Organizations of Medical Sciences (CIOMS) and WHO are described in table 2.2

Table 2.2 Cause-specific categorization of AEFI (CIOMS/WHO 2012)

Cause-specifictypeofAEFI	**Definition**
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Immunization error-related reaction (formerly “programme error”)	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

2.2.1. Vaccine Reactions

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

a. *Cause-specific vaccine reactions*:
   - Vaccine product-related reaction and
   - Vaccine quality defect-related reaction

b. Vaccine reactions by seriousness and frequency:

- Common or minor reactions;
- Rare or serious reactions.

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 agent (e.g. wild polio virus) during the manufacturing process or contamination introduced during the manufacturing process could cause the 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 2.3 describes the frequency of occurrence of reported adverse events.

Table 2.3 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, minor vaccine reactions*

They are caused when recipient's immune system reacts to antigens or the vaccine's components (e.g. aluminium adjuvant, stabilizers or preservatives) contained in the vaccine. Most AEFI are minor and settle on their own. Minor AEFI could be local or systemic. Local reactions include pain, swelling and redness at injection site. Systemic reactions include fever, irritability and malaise. A successful vaccine reduces these reactions to a minimum while producing the best possible immunity. Table 2.4 describes the common minor vaccine reactions by antigen and the treatment for the same.

Table 2.4 Common minor vaccine reactions by antigen and treatment

Vaccine	Local adverse events (pain, swelling, redness)	Fever (> 38^0C)	Irritability, malaise and systemic symptoms
BCG[1]	90%-95%	-	-
Hepatitis B	Adults up to 15% Children up to 5%	1 – 6%	-
Hib	5-15%	2%-10%	
Measles/MR/MMR	~10%	5%-15%	5% (Rash)
OPV	None	Less than 1%	Less than 1%[2]
Pertussis (DTwP)[3]	up to 50%	up to 50%	up to 55%
†Pneumococcal conjugate	~20%	~20%	~20%
Tetanus/DT/aTd	~ 10%[4]	~ 10%	~ 25%
Treatment	Cold cloth at injection site and Paracetamol*	Give extra oral fluids, wear cool clothing, tepid sponge or bath and Paracetamol*	Supportive treatment

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

[2] Diarrhoea, Headache and/or muscle pains

[3] When compared with whole cell pertussis (DTwP) vaccine, acellular pertussis (DTaP) vaccine rates are lower.

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

* Paracetamol dose: up to 15mg/kg every 6-8 hours, maximum of 4 doses in 24 hours

† Source: http://www.cdc.gov/vaccines/pubs/ACIP-list.htm

- ***Rare, more severe (and serious) vaccine reactions***

They are caused by the body's reaction to a particular component in a vaccine. The term “severe” is used to describe the intensity of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance. Severe AEFI can be disabling but is rarely life threatening. Some examples are seizures, thrombocytopenia, Hypotonic Hypo-responsive Episodes (HHE), prolonged crying etc.

Severe AEFI 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

Note: *ALL serious AEFI should be reported, investigated and the causality assessed*

The rate of occurrence of the rare and more serious reactions has been summarized in table 2.5. Note that children less than six months or over six years of age are unlikely to have febrile seizures. If this happens, a thorough investigation should be conducted to determine the underlying cause(s).

Table 2.5 Severe 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
Hib	None		
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	VAPP	4-30 days	0.4 - 3[2]
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[3]
	Hypotonic, hypo responsive episode(HHE)	0-48 hours	30-990

Vaccine	Reaction	Onset Interval	Rate per million (1,000,000) doses
	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
Pneumococcal Conjugate Vaccine (PCV10)	None	-	-
Inactivated Polio Vaccine(IPV)	None		

Notes

1. *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*

2. 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.

3. 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

The term “Immunization” as used here means the “use” of a vaccine for the purpose of immunizing individuals. “Use” includes all processes that occur after a vaccine product has left the manufacturing/packaging site – i.e. handling, prescribing and administration of the vaccine.

Immunization error-related reactions are usually preventable and they divert attention from the benefit of the immunization program. Some of them are described in Table 2.6. The identification and correction of these errors in a timely manner are, therefore, of great importance.

Table 2.6 Immunization error-related reactions

Immunization error		Related reaction
Error in vaccine handling:	Exposure to excess heat or cold as a result of inappropriate transport, storage or handling of the vaccine (and its diluents where applicable)	Systemic or local reactions due to changes in the physical nature of the vaccine, such as agglutination of aluminium-based excipients in freeze-sensitive vaccines
	Use of a product after the expiry date	Failure to protect as a result of loss of potency or 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 boneinjury 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

An immunization error-related reaction may sometimes lead to a cluster of events associated with immunization. These clusters are usually linked to a particular provider or health facility, or even to single or multiple vials of vaccine that have been contaminated or inappropriately prepared. For instance, freezing vaccine during transport may lead to an increase in local reactions. The details of an approach to investigating AEFI clusters are described later.

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. Hyperventilation as a result of anxiety about the immunization leads to specific symptoms such as light-headedness, dizziness, tingling around the mouth and in the hands. This is also common in mass vaccination campaigns.

Younger children may have breath-holding and vomiting as a common symptom of anxiety. Young children may also scream or run away to avoid the injection.

Some individuals may have needle-phobia. In group immunization, mass hysteria is possible, especially if one or more of the vaccine recipients observed by others to faint or have some other reaction such as itching, weakness of limbs and so on.

Sometimes a fainting episode can be misdiagnosed as anaphylaxis. Careful observation and clinical judgments is necessary to differentiate.

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 in a mass immunization campaign.

Vaccines are normally administered early in life when infections and other illnesses are common, including manifestations of underlying congenital or neurological conditions. It is, therefore, possible to encounter many events, including deaths that can be falsely attributed to vaccine through a chance association.

For example, 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.

A calculation is shown in Table 2.7relating to the incidence of infant (under one year) deaths in selected countries to the number of deaths temporally associated with routine DTP or pentavalent vaccine (PVV) immunization. As shown, infant mortality rates result in coincidental deaths in the day, week and month after immunization which are only temporally related to immunization. The actual number of coincidental deaths depends on the population size and infant mortality rate.

Table 2.7 Estimated numbers of coincidental infant deaths that could be temporally linked to immunization (for example with DPT/PVV) in the month, week and day after immunization in selected countries

Country	Infant mortality rate per 1000 live births (IMR)	Number of births per year (N)	Estimated number of infant deaths in			Estimated number of PVV/DTP immunizations* in		
			a month	a week	a day	a month	a week	a day
Bhutan	42	15 000	53	12	2	3233	746	106
Canada	5	388 000	162	37	5	86 864	20 045	2856
China	13	16 364 000	17 728	4091	583	3 634 035	838 624	119 475
Ethiopia	48							
Indonesia	25	4 331 000	9023	2082	297	950 113	219 257	31 237
Iran	21	1 255 000	2196	507	72	276 445	63 795	9089
Mexico	13	2 195 000	2378	549	78	487 455	112 490	16 026
Sudan	57	1 477 000	7016	1619	231	313 382	72 319	10 303
United Kingdom	4	761 000	254	59	8	170 540	39 355	5607

3. Prevention and management of AEFI

3.1. General principles of prevention and management of AEFI

i. 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.

ii. Vaccine anaphylaxis is very rare. However, it is recommended that preparedness to provide emergency treatment for anaphylaxis is necessary in all clinic settings. All immunization providers need to be trained and develop competence in recognizing and managing anaphylaxis and have epinephrine (adrenaline) available.

iii. 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 severe symptoms. Such action will help to reassure parents about immunization and prepare them for common reactionsand to adhere to subsequent vaccination schedules as well.

iv. 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.

v. 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 because of 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 that 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, diarrhea, 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 aluminium-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 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 clearly aware of such contraindications and any precautions. Any uncertainty should be referred to a higher level – a program manager, pediatrician 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.

Health-care workers 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 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 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.

Careful observation and clinical judgment to differentiate between anaphylaxis and syncope is necessary. However, an accidental administration of a single dose of adrenaline (intramuscularly) to a vaccine recipientwith only syncope does not harm the vaccine recipient.

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 12 cases per million vaccine doses.

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 is the reaction.

Events happen without warning. Emergency equipment must be immediately at hand whenever immunizations are given. All vaccinators must be familiar with the practical steps necessary to save life following anaphylaxis. Each vaccinating centre must have an emergency kit with adrenaline. 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. It is important to note that health-care workers may misdiagnose syncope attack as anaphylaxis and administer adrenaline as a part of the emergency care. If the correct dose of adrenaline according to age and weight is administered via the intramuscular route, no harm is likely to occur. However, an overdose, by administering intravenous or intracardiac adrenaline or by repeated administration, may cause harm.

For all cases of suspected anaphylaxis it is important that all symptoms and signs are well documented by health-care providers. Because anaphylaxis is very rare, other causes of sudden and severe symptoms post-immunization that is more common than anaphylaxis need to be considered. Table 2.7 lists conditions which may be mistaken for anaphylaxis.

Table 3.1 Conditions that may be mistaken for anaphylaxis post-immunization

Diagnosis	Onset: symptoms and signs
Vasovagal event	Symptoms are usually immediate (< 5minutes) and commence during the injection process. No skin rash, bradycardia not tachycardia, no respiratory involvement, spontaneous resolution when prone.
Hypotonic hyporesponsive episode	Onset 2-6hours post-immunization, sudden pallor, hypotonia and unresponsiveness, usually in an infant. No skin rash, 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 apnea 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 infant. 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 cause.
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.

4. AEFI Surveillance in Ethiopia

Surveillance for adverse events following immunization (AEFI) is an integral part of the National Pharmacovigilance Activities, and reinforces the safe use of all vaccines in the country while also helping to maintain public confidence in its immunization program. As shown in fig 4.1, this is done systematically.

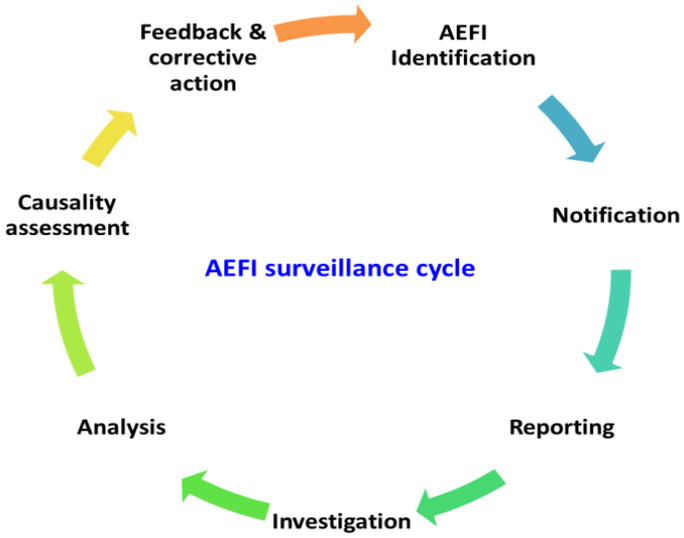


Fig 4.1 AEFI surveillance cycle

4.1. Objectives of the AEFI Surveillance System

General Objective

To early detect and appropriately respond to adverse events following immunization in order to reduce the negative impact on the health of the individuals and on the immunization programstherebyenhancingprogram credibility and to provide country-specific data on vaccine risks.

Specific Objectives

- To rapidly detect and respond on time to occurrence of any adverse event
- To trigger further clinical, epidemiologic, or laboratory investigations regarding a possible causal relationship between a vaccine and adverse event
- To provide descriptive epidemiologic data on national numbers of reported adverse events following immunization (AEFI) to identify risk factors and mechanism of actions
- To closely monitor the safety of newly licensed vaccines
- To detect previously unrecognized reactions from both existing and newly licensed vaccines
- To detect apparent increases or decreases in previously reported events

- To detect preexisting conditions that may promote reactions and may represent contraindications or precautions to additional doses, in addition to that it prevents false blaming arising from coincidental AEFI.
- To detect vaccine lots associated with unusual numbers and types of reported events
- To detect, correct and prevent immunization error-related AEFIs caused by errors in vaccine preparation, handling, storage or administration
- To effectively communicate with parents, community, the media and other stake holders to create awareness on AEFIs without jeopardizing the immunization programcredibility.
- To collaborate and share information with WHO (through post-marketing surveillance), to support generation ofnew and additional information on vaccine safety.

Vaccine recipients themselves and/ or parents of immunized infants/children, health care providers at immunization facilities are most likely to recognize or detect AEFIs when they first occur. Any AEFI case that is notified to any health care provider working within the health care system, should be reported to the WoredaEPIOfficer (WEO) using the standard reporting form (Annex 1) through the fastest means possible. The WEOshould in fact be informed of any Serious AEFI cases by telephone and this should be followed up by completion and submission of the reporting form.

The **reportable AEFI** include:

- Serious AEFI,
- AEFI as a result of potential immunization errors,
- Clusters,
- AEFI causing parental or community concern resulting in the family notifying the case back to the healthcare system,
- Those that are unexpected, and
- Those that are known but occur with unexpected frequency.

Table 4.1 below provides case definitions of commonly reportable AEFI. However it needs to be stressed that health workers should report all cases that are notified to them.

Table 4.1 Case definitions of the reportable adverse events.

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), - **Respiratory** – persistent cough, wheeze, stridor, - **Cardiovascular** – low blood pressure (hypotension) or reduced circulation (fast weak pulses), - **Gastrointestinal** – vomiting, abdominal pain.	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	Acute onset of major illness characterized by depressed or altered level of consciousness and/or distinct change in behaviour lasting for one day or more	Measles, Pertussis
Fever	The fever can be classified (based on rectal temperature) such as • Mild fever: 100.4 ^{0}F to 102 ^{0}F (38 to 38.9oC), • Moderate fever: 102 ^{0}F to 104.7^{0}F (39 to 40.4^{0}C) and • Severe fever: 104.7^{0}F or higher (>40.5^{0}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) • 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. Sterile abscesses are usually due to the inherent properties of the vaccine.	All injectable vaccines

AEFI	Case definition	Vaccine
Intussusception	An infant who received one or more dose of Rota Vaccine in the last 21 days and presented with two major criteria; **or** one major criterionand three minor criteria: ***Major criteria:*** **1) Evidence of intestinal obstruction** — History of bile-stained vomiting ***and either*** — examination findings of acute abdominal distension and abnormal or absent bowel sounds ***or*** — plain abdominal radiograph showing fluid levels ***AND*** dilated bowel loops. **2) Features of intestinal invagination** One or more of the following: abdominal mass; rectal mass; intestinal prolapse; plain abdominal radiograph showing a visible intussusceptum or soft tissue mass; abdominal ultrasound showing a visible intussusceptum or soft tissue mass; abdominal CT scan showing a visible intussusceptum or soft tissue mass. **3) Evidence of intestinal vascular compromise or venous congestion**: Passage of blood per rectum; ***or*** passage of a stool containing "redcurrant jelly" material; ***or*** blood detected on rectal examination. ***Minor criteria:*** Predisposing factors: age <1 year and male sex; abdominal pain; vomiting[1]; lethargy[2]; pallor[2]; hypovolemic shock; plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern. NB: In an infant who received Rota Vaccine in the last 21 days, where the service is available, the demonstration of invagination of the intestine at surgery **and/or** 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[1] that is proven to be **reduced** by hydrostatic enema on **postreduction ultrasound**; **and/or**the demonstration of invagination of the intestine on autopsy can be considered as confirmatory for intussusception .	Rota
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 highpitched 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

AEFI	Case definition	Vaccine
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
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
Serious AEFI: Any AEFI causing • Death • Hospitalization • Disability, congenital anomaly • Other severe and unusual events		No time limit, if they are thought by health workers or the public to be related to immunization

All vaccination staff members must be able to recognize and report AEFIs . However, accurate diagnosis of AEFIs requires staff training and education. Health care providers also have the additional responsibility to manage AEFI and, if necessary, refer such patients for any required medical management.

4.2 Stakeholders 'Roles and Responsibilities in AEFI Reporting and Investigation

AEFI surveillance systems exist at national and international levels to ensure effective monitoring and prompt actions in response to AEFIs. AEFI surveillance in Ethiopia needs to be a collaborative venture between the EFMHACA, the National EPIprograms of FMoH, PHEM/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, clients including guardians and all concerned development partners as all are responsible for the safety of vaccines.

EFMHACA 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 FMOH 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. The successful implementation of AEFI surveillance system requires active involvement of EFMHACA, immunization program of the FMOH and other stakeholders. EFMHACA and the national EPIprogram of the FMOH are the two main actors for developing and running effective AEFI surveillance system in the country. In this regard a close collaboration in the process of AEFI surveillance supported by all stakeholders is needed. Others such as causality assessment committee, academic institutions are also important for successful implementation of AEFI surveillance.

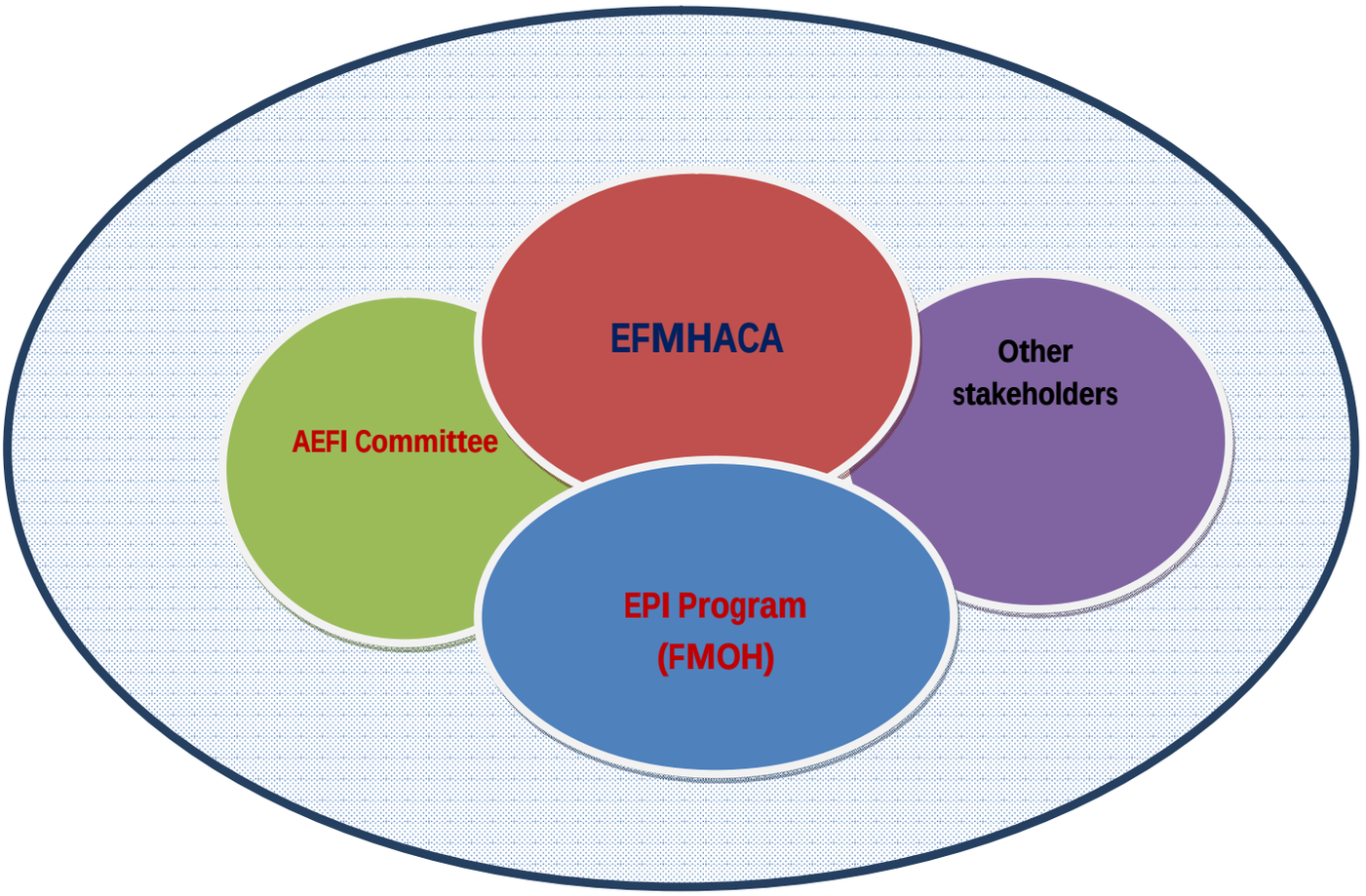


Figure 4.2: AEFI surveillance stakeholders

SubnationalStakeholders in AEFI reporting and investigation are:

- Parents/ guardian
- Health workers
- The WoredaEPI Officer (WEO) and Woreda Rapid Response Team
- The regional EPIOfficer (REO)
- The Branch EFMHACA pharmacovigilance focal person
- The regional AEFI Taskforce

National stakeholders in AEFI investigation

- FMoH EPI
- EFMHACA
- National AEFI committee
- PHEM/EPHI

4.2.1. Rolesand Responsibilities of the Subnational Stakeholders

The parent/ guardian

At the time of immunization, it is important for health workers to sensitize the parents about expected events such as fever and pain at injection site, etc. following immunization. Parents should be advised about simple home remedies (e.g. correct positioning of the child when sleeping, increasing intake of fluids, sponging, breast feeding, antipyretics etc.) should such events occur; however, at the same time, they should also be instructed to report to the health worker severe expected events (e.g. very high fever not responding to anti pyretic) or other unusual events if they occur.

The health worker

Health workers should advise vaccine recipients or their parents/care givers about simple home remedies (e.g. correct positioning of the child when sleeping, increasing intake of fluids, sponging, breast feeding, antipyretics etc.) should such events occur.If home remedies do not work, vaccine recipients themselves and/ or parents or guardians of immunized infants/children should be advised to report the event to healthcare providers at immunization or other healthcare facilities. Sometimes staff in these facilities recognizes or detects AEFIs when they first occur. All such AEFI cases brought to the notice of the healthcare worker or detected by the worker should be reported to the WoredaEPIOfficer (WEO) using the standard reporting form (Annex 1).This form captures critical information related to the patient, vaccines and diluents, signs and symptoms, and outcome of the AEFI.The health worker is responsible to maintain complete records of the vaccine and diluent given, time of administration, etc.

Thus the main role of the health worker is to provide due advice to vaccine recipients and their caregivers, provide primary medical care and report the basic details about the notified adverse event to the woreda by completing the AEFI reporting form (preceded if appropriate with a preliminary report by telephone for a serious event).

Woreda, Zonal and the Regional levels

When an AEFI report (Annex 1) is received by the WEO, s/he should review the report and determine if the reported AEFI case meets the criteria required for a detailed investigation. If necessary s/he should contact the primary reporter and visit the locality of the event and interview relevant stakeholders for additional information. The case may be considered

- Not warranting detailed investigation if it is a minor AEFI and NOT serious AEFI, WEOshould indicate this on the reporting form and email/ fax the same to the concerned zonal EPI Officer,

The Zonal EPI Officer will report to, regionalEPIOfficer (REO) and, then, s/he will report tothe National EPITeam Leader.

All serious AEFI should be investigated and a completed AEFI investigation form (Annex 3) routed to the national level. The details of each case should be included in the woreda and regional line list.

At the regional level, the REO also reports the case to Branch EFMHACA pharmacovigilance focal person. At the national level, the National EPI Team leader will report to the NationalPharmacovigilance Team Leaderin the regulatory@fmhaca.gov.et

Warranting a detailed investigation if it is a Serious AEFI (death, hospitalization, significant disability, life threatening, or congenital anomaly/ birth defect) or is a part of a cluster, or a part of a group of events above expected rate/ severity, or a suspected signal, WEOshould discuss the same with the local experts like rapid response team members (or technical expert committee if available) and plan for a detailed field investigation. Prior to initiating an investigation, s/he should send (e.g. through e-mail) the report (Annex 1) to the zonal/regional levels as described above.

If the WEOand the experts feel that the investigation can be done locally, they can visit the patient and locality, initiate the detailed investigation along with appropriate members of the local healthcare team. If however assistance is required for investigation from the zonal, regionalor national level, therespective EPI officers should be contacted and assistance for an investigation can be solicited. National investigations should be led by a team from the national Pharmacovigilance Centersupported by the EPI and National AEFI Committee. During field investigations, the AEFI investigation form (Annex 3) should be used as a guide to collect suitable information.

The investigators should seek to document any deficiencies found in a generic way and suggest corrective measures, and not single out any individuals to blame. While an individual may have been at fault, it is more effective to focus on identifying the problems in the system and procedures leading to the event. This is more effective in avoiding similar errors in the future, than blaming or punishing individuals. Such an approach is essential to ensure that AEFI reporting is encouraged for the ultimate benefit of all patients and the immunization program as a whole. It is also much more likely to improve system performance. Errors provide opportunity for learning and creating a system that encourages continued improvement. Hiding errors will only serve to form the basis for more errors.

The specific activities conducted at this point will include the following

- Confirm the AEFI, assign a unique report identifying number, complete ALL details in the AEFI reporting form (in case any of them were missing when reporting) and initiate AEFI investigation.

- Convene a local clinical experts (or woreda rapid response team if available) planning meeting prior to the investigation.
- With the experts, the WEOshould visit as required the patient, the care provider(s) and the hospital; interview relevant stakeholders (parents, health worker, treating doctor, vaccine supply focal person, etc.); and conduct the investigation of the AEFI case.
- Complete the AEFI investigation form (Annex 3).
- Initiate collection of medical reports, a post-mortem report (if available), used vaccine vials (if possible, and kept under cold chain conditions), logistic samples, and laboratory reports e.g. CSF, serum (or other biological products).

Generally before the AEFI is attributed to any vaccine product related problems, the investigation team should rule out any potential immunization errors and obvious coincidental events, as these are more common. Therefore, the investigation should first try to rule out immunization errors related to the storage, handling, reconstitution or administration of vaccines.

Attention can then focus on other events. Details of coincidental events can be determined by reviewing hospital admissions for similar conditions during the same period and verifying their vaccination status. A quick review of the morbidity pattern of similar conditions in the previous years can also indicate if the event is a part of a similar pattern observed in the previous years. The medical literature can also help, as the estimated background incidence of various conditions may be available in the published domain.

Once the investigation is initiated, the Woreda / Zonal/Regional investigation team should inform the EPI and EFMHACA on the status and progress of the investigation. This is necessary, as a national level EFMHACA public relations officer should be the spokesperson of the government to the media and the public about the investigation. The completed case investigation form (annex 3) along with the supporting documents such as the medical report, vaccine, logistic samples, laboratory reports e.g. CSF, Serum (or other biological products) should be sent to the EPI andEFMHACA **within 7 days** of initial case notification. If this is not possible, at least a progress report should be made with details on when the completed report can be expected.

It is important to remember that in case Regional or national assistance for an investigation is requested, more accurate information can be obtained by a single coordinated investigation rather than a piecemeal investigation. Table 4.2 summarizes the key steps in an AEFI investigation.

Investigator(s) may use the “WHO Aide Memoire on AEFI Investigation” as a guide. This is available at www.who.int.immunization_safety/en

Table 4.2 Steps in an AEFI investigation

	Step	**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 the information. • Obtain any details missing from AEFI Report Form.
2	Investigate and collect data:	
	About the patient:	• Immunization history

	Step	Actions
		• Previous medical history, including prior history of similar reaction or other allergies • Family history of similar events.
	About the event:	• History, clinical description, any relevant laboratory results about the AEFI and diagnosis of the event • Treatment, whether hospitalized and outcome.
	About the suspected vaccine(s):	• Conditions under which the vaccine was shipped, its present storage condition, state of vaccine vial monitor and temperature record of refrigerator • Storage condition of vaccine at all levels before it arrived at health facility, Vaccine Vial Monitor. • The date of manufacture, lot and batch numbers of vaccine and diluent
	About other people:	• Whether others received the same vaccine and developed illness and whether they need to be included in the investigation. • Whether others had similar illness (may need working case definition); if so exposure of cases to suspect vaccine(s) • Discuss with other immunization service providers to obtain an idea of the local standard practices
3	Assess the service provided by asking about:	• Vaccine storage (including open vials), distribution and disposal • Diluents storage and distribution • Reconstitution(process and time kept) • Use and sterilization of syringes and needles • Number of immunizations (greater than normal?) • Details of training in immunization practice, supervision and vaccinator(s)
	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 into the syringe, injection technique, safety of needles and syringes; disposal of opened vials) • If 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 working hypothesis? • Laboratory tests may help (see text).
6	Conclude investigation	• Reach a conclusion on the cause. • Complete AEFI Investigation Form • Take corrective action and recommend further action.

4.2.2. The National level Stakeholders

When the EPITeam Leader and/or the pharmacovigilance Team Leader in EFMHACAreceivesthe filled AEFI reporting form, it is essential to review it in the context of other reported AEFI received from all parts of the country, particularly in the same period of time, to see if this report may constitute a signal. This can be done by appending data into a national AEFI line list (Annex 2) with information from the reporting form and reviewing the data or running analyses as needed. If similar cases were reported earlier, it is essential to determine if an epidemiological linkage or other pattern can be identified if there is one. The need for technical or operational assistance for the investigation has to be assessed. Expert advice can be sought from the National AEFI Committee at this point.

The EFMHACA pharmacovigilance center(PVC)and the National AEFI Committee play a key role in supporting the immunization program for AEFI investigation and causality assessment. They also provide recommendations to the National Immunization Technical Advisory Group (NITAG), the FMoH and EPI on vaccines based on their causality assessment findings. The EFMHACA-PVC constitutes the National AEFI secretariat and it coordinates and provides technical/logistical support to conduct the meetings of the National AEFI Committee (Fig 4.2).

EPI and PVCare responsible for providing all feedback to the relevant stakeholders at the national, regional, zonaland woreda levels within 7 days of causality assessment or potential signals determined by data review/analysis at the national level. They are also responsible on following up on the actions recommended at the national and regionallevel (e.g. change in logistics, cold chain, training after immunizationerrors etc.) and ensuring that they are implemented.

The EFMHACA or the national pharmacovigilance centre is responsible to share the information with the global community by uploading the information into the Global pharmacovigilance database – VigiBase®, maintained by the Uppsala Monitoring Centre under the WHO International Drug Monitoring Program – using information available in the completed case investigation form(annex 3). A copy of the uploaded case details in VigiBase® should be provided to EPI on a monthly basis. EFMHACA can also provide information on the vaccines and lots distributed in the country when requested by the AEFIcommittee, EPI and the Ethiopian National Immunization Technical Advisory Group (NITAG). The EFMHACA can also provide additional information on AEFI from other sources. Cases shared by EFMHACA to EPI should be a part of the total AEFI cases documented by EPI in the WHO-UNICEF Joint Reporting Form (JRF).

4.2.2.1. Ethiopian Food, Medicine and Healthcare Administration and Control Authority (EFMHACA)

EFMHACA has the mandate of ensuring that every pharmaceutical products (including vaccines) used within the country is of good quality, effective, and safe for the purposes for which it is proposed. Therefore; EFMHACA is responsible for the following activities regarding AEFI surveillance:

- Designing, establishing, maintaining and evaluating AEFI surveillance system in the country in collaboration with FMOH /EPI and other stakeholders
- Revising ,updating and distributing AEFI surveillance reporting tools and guidelines

- Ensuring accessibility of tools (AEFI Reporting Form; Guidelines etc.) to the Regional Health Bureau for further distribution to zonal and woreda levels
- Constituting an Expert Committee to evaluate AEFI reports and assess causality
- Maintaining and ensuring the use of database at the National level.
- Share the updated line list with EPI Team Leader and WHO Country Office on regular basis
- Provision and follow up of training of personnel involved in AEFI surveillance in collaboration with other stakeholders.
- Analyzing and providing feedback to EPI, healthcare professionals, caregivers and other stakeholders on the AEFI reports
- Monitoring the effectiveness of the AEFI surveillance system
- Conducting supportive supervision of AEFI surveillance activities
- Establishing a coordination platform of stakeholders through bimonthly(once every two months) AEFI partners coordination meetings
- Sharing information with international agencies and manufacturers
- Carrying out risk- benefit analysis of vaccine used in the immunization program
- Taking the necessary corrective measures when there is a safety and quality problem of vaccine is observed.
- Communicating AEFI and immunization safety that needs public attention at the National level with FMOH.
- Supporting regions and strengthening AEFI documentation and reporting system.
- As member of EPI taskforce, EFMHACA should participate in the planning, training, implementation and monitoring phases of immunization campaigns and new vaccine introductions.

4.2.2.2. NationalImmunization Program of FMOH

In the National AEFI surveillance system, EPI/FMOH is responsible for :

- Collaborating with EFMHACA in the continuous development ,revision and distribution of tools and guidelines for AEFI surveillance
- Ensuring further distribution of tools (AEFI Reporting Form; Guidelines etc.) from the Regional Health Bureaus to lower levels
- Training of peripheral level health staff on AEFI activities and case management in collaboration with regional and zonal health bureau.
- Providing support to Region, Zone and Woreda on AEFI reporting and investigations as needed
- Submitting AEFI reports received from routine immunization and campaigns to EFMHACA as soon as possible.

- Strengthening AEFI documentation and reporting systemthrough the routine immunization, supplemental immunization activities as well as during new vaccine introductions.
- Ensure participation of EFMHACA in the planning, training, implementation and monitoring phases of immunization campaigns and new vaccine introductions.

4.2.2.3. EPI and Regulatory bodies at different levels (Regional, Zonal,Woreda)and Branch EFMHACA

- Monitoring of timely reporting of AEFI cases by health professionals by EPI
- Collaboration with regional health bureau EPI Officerand Branch EFMHACAon AEFI
- EPI to collaborate with EFMHACA on sharing of AEFI related information, training materials and manuals
- EFMHACA together with EPI to give orientation and training to health workers on AEFI monitoring.
- EPI is to lead handling and timely dissemination of well-organized information to community on timely bases.
- EPI to Advise and make strict follow up to the parent/client to return or seek medical attention to allow detection of an AEFI by EPI.
- Regulatory bodies at different levelscapturingADRs should also share AEFI reports(if available to them) to the respective EPI counterpart at the woreda, zonal and regional levels

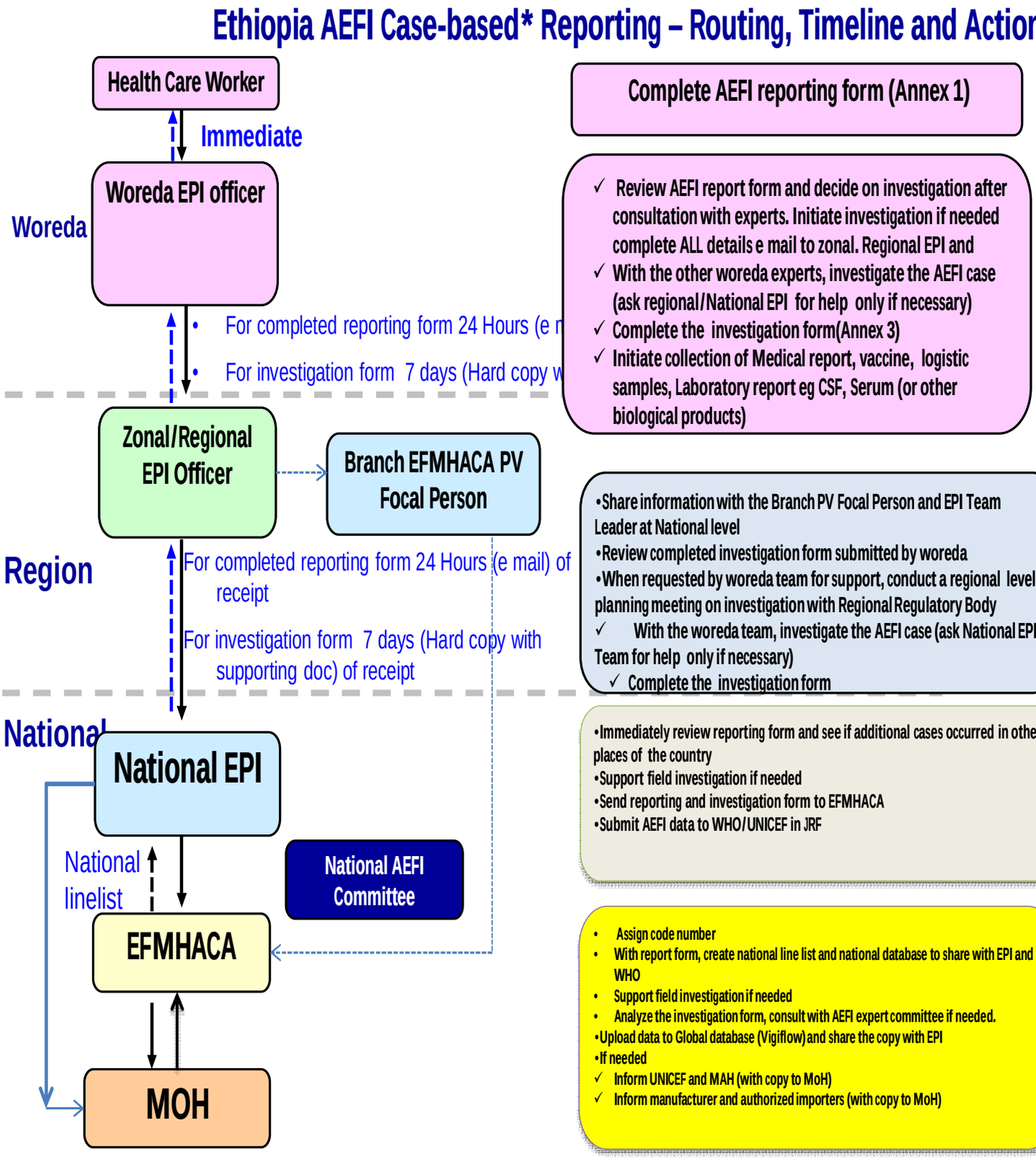


Figure 4.3Ethiopia AEFI Reporting – Routing, Timeline and Actions

5. Investigating AEFIs

The report of an AEFI will usually be followed by a case investigation or, when there is a cluster of AEFIs, by a series of case investigations. The ultimate goal of a case investigation is to find the cause of an AEFI or cluster of AEFIs and thereafter conduct follow-up activities. Investigation should identify any immunization related errors or vaccine product related reactions because these are preventable, and if co-incidental events are recognized then demonstrating this will be important to maintain public confidence in the Immunization Program.

5.1. Objectives of AEFI investigation

The investigation of AEFI report is critical in identifying and correcting the problem(s) in order to ensure trust among clientsand the different EPI actors.

General Objective

- To seek detailed information of anadverse event and take appropriate correctiveactions to maintain public confidence in the immunization program and the products circulating in the market.

Specific objectives

- To identify the cause of AEFI
- To confirm the reported diagnosis or establish a diagnosis.
- To document the outcome of the reported adverse event.
- Prevent false blame from coincidental events
- To identify the details of vaccine (s) administered and to determine the timing between administration of the vaccine and the onset of the event.
- To 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.
- To 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.
- To determine whether similar events are occurring in individuals who have not received the same vaccine
- Maintain confidence by properly responding to parent/community concerns while increasing awareness (public and professional) about vaccine risks
- Generate new hypotheses about vaccine reactions that are specific to the population

- Estimate rates of occurrence on AEFI in the local population, compared with trial and international data (particularly for new vaccines being introduced).

5.2. What should be investigated and when?

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

- All serious cases of AEFIs
- Clusters and events above the expected rate and severity
- Evaluation of suspected signals
- Other AEFIs

✓ Immunization error is suspected (e.g. injection site abscesses, sepsis)

✓ Significant events of unexpected cause within 30 days of vaccination

✓ Events causing significant parental and community concerns (e.g. febrile seizures, hypotonic hypo-responsive episode)

Please note that any significant adverse event following vaccination should be reported and investigated irrespective of the time interval between vaccination and onset of symptoms.

5.3. Who should be involved in AEFI investigation?

The health worker will complete the AEFI**Reporting Form (Annex 1)** and report to WEO. The WEO along with the woreda rapid response team (RRT)will carry out the investigation.. The availability of the RRT within the PHEM structure will be an opportunity to further exploit for investigation of AEFI cases since they have experience in other epidemiological investigation. Expert support from zonal to national levels and close communication among all levels are important.

EFMHACA, national AEFI Committee, National EPI, regional AEFI task forces and zonal regulatory bodies are expected to support investigation ofthe case according to their capacity at their level if desired by WEO. Technical supports from partner organizations like WHO may be sought as and when needed.

5.4. When to investigate?

Investigation should begin as soon as possible, ideally in24 hours but maximum within seven days of notificationto the health worker, to identify any immunization error(s) that might be present, to 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.

5.5. What data should be collected?

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.

5.6. How should data be collected and recorded?

Methods to determine the cause of the AEFI should include the following: clinical examinations; interviews with the client or care giver; review of patient registers; observation of immunization administration, vaccine handling, and storage; examination of health facility records and laboratory reports.

The investigation team would be provided with the filled AEFI Report Form as submitted by the healthcare worker. The AEFI report provides a historical record of the AEFI and summarizes the findings and conclusions about an AEFI case or cluster of cases.

5.7. How to investigate AEFI?

An AEFI investigation follows standard epidemiological investigation principles (Figure 2). It is important to investigate suspected adverse events promptly and completely. The investigator will need to look directly at the reported reaction as well as gather information from the client/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be recorded on an AEFI Investigation Form (Annex 3).

Immunization related errors and coincidences are the most likely causes of adverse events. Therefore, the investigator should suspect immunization errors as the cause and examine the evidence for any errors in the storage, handling, or administration of vaccines. Attention can then focus on finding out more about the particular error and taking the necessary corrective action. The investigators should seek to identify system problems rather than to find individuals to blame. For example, the investigation may reveal that more abscesses are reported in one immunization clinic due to faulty immunization technique by a health care worker. In such case, rather than blaming the health care worker, the investigators should find reasons for why health care worker practice incorrect technique, which may be a system failure such as lack of training, lack of supportive supervision etc.

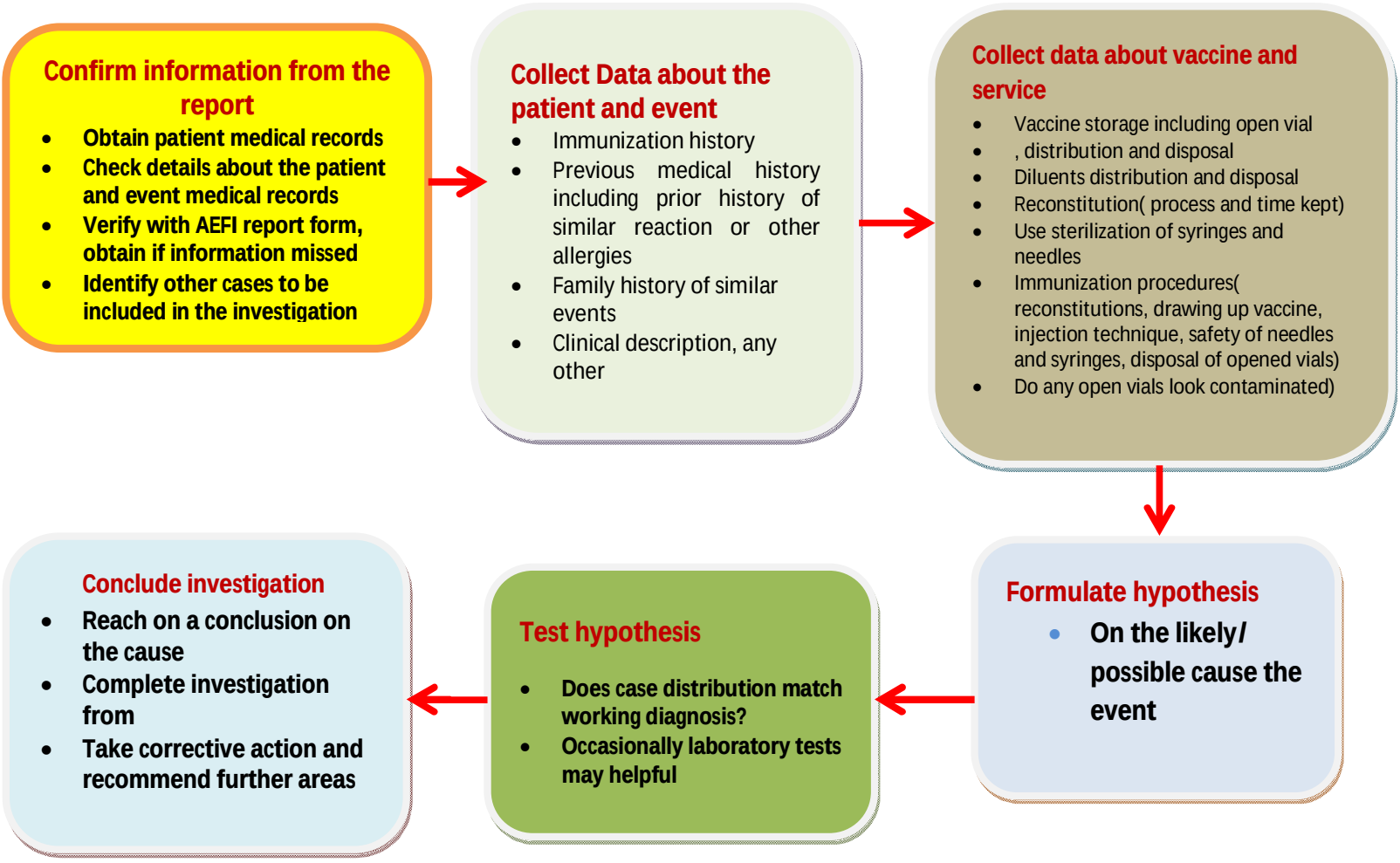


Figure 5.1 Steps in AEFI Investigation

Clear case definitions, from the guidelines on reporting or defined during the investigation, are essential. The investigation needs to identify all cases in the community and find out the outcomes for all who received the suspect vaccine. The risk of adverse eventshould be compared for those who received the vaccine versus those who did not.

The most important 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.

5.8. Investigation of AEFI with fatal outcome

In the event of an identified death following immunization, the field investigation has to be initiated immediately. Within 24 hoursthe death should be notified to all administrative levels concerned, including the Woreda, Zonal and RegionalEPIofficers, the National EPI and the EFMHACA. Investigation of the case should be carried out by a team of experts from relevant areas, including clinicians. As a death causally linked to immunization is extremely rare (anaphylactic reactions being one of the only 2-3 known events), major immunizationerrors may be involved and thus an investigation to rule those out has to be conducted without any delay to prevent additional cases. As

any fatality temporally linked to a vaccination can cause panic, the public will also demand an immediate explanation.

A post mortem examination is preferred and recommended following all deaths suspected to be caused by a vaccine / immunization. However, the decision to conduct a postmortem should be within the religious, cultural acceptance and legal framework of the local population.

5.9. 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) is done by gathering details (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 workers' 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. 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.

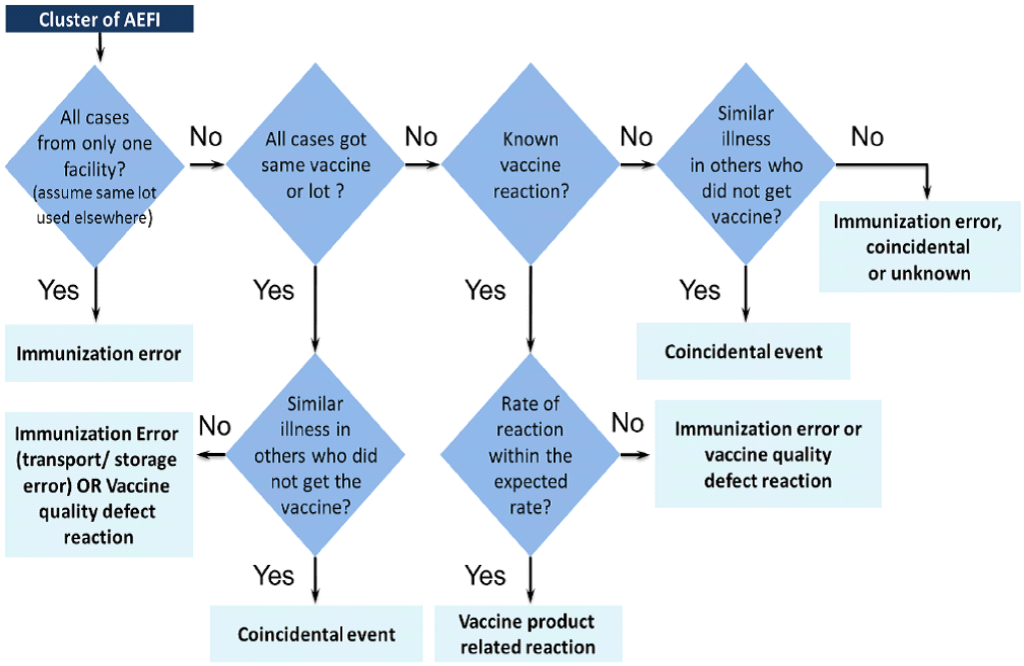


Fig 5.2 Identifying cause of AEFI cluster

For relatively new vaccines or established vaccines used in new target populations, a cluster may represent a previously unrecognized vaccine product-related reaction. Knowledge of the background incidence of events which may occur in causal relationship with a vaccine is therefore essential for assessing a cluster in terms of the strength of the signal it may provide.

6. 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 logistics used.

Laboratory tests for the purpose of AEFI case diagnosis and case management conducted on the patient (eg 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 as described in section 7.2.

Laboratory testing of samples of vaccines and logistics are rarely necessary. It is not mandatory following an AEFI, particularly if the cause is evident such as a coincidental event or an immunization error. However, laboratory testing of vaccines and logistics are at times required to confirm or rule out the suspected cause.

In the context of AEFI, sometimes additional specific tests on the patient, vaccines and logistics as outlined below may also be necessary to confirm the cause. The testing of additional specimens includes:

Human specimens

- Histopathology, body fluids etc. can be done at laboratories identified and approved by the EFMHACA.

- Autopsy specimens at approved and accredited government forensic laboratories as identified by MoH

Vaccines and logistics

- Vaccines and diluents for sterility and chemical composition.
- Syringes and needles for sterility.

Only the appropriate specimen in the correct quantity required for the investigation should be collected. Laboratory specimens should be stored and transported as recommended and accompanied by clear supporting documents, reasons for specimen collection and any additional information required by the investigators. In case laboratory investigation is required, AEFI laboratory request form (Annex 4) should be completed and sent with any specimen collected.

6.1. Human Specimens

It is difficult to generalize what specimens will be required in a given situation as it will depend on the symptoms and signs of the patient and the clinical decisions made by the health professional in charge of the case. Table 6.1 gives a general outline of some of the specimens that could be collected. The list is not exhaustive. It is necessary to record the type date and time of collection of each and every sample collected. Documents of clinical investigations and medical records related to the incident will support correct lab investigations. It is advised to consult the treating clinician(s) to make a decision on samples to be tested.

For biochemical, histo-pathological and microbiological examination, specimens should be handled at the health facility and forwarded to the nearest laboratory, where facilities are available to carry out requested laboratory testing. If facilities for essential laboratory testing are not available at intermediate level (Regional/Zonal/Woreda) institutions, sending samples to national laboratory or an accredited laboratory abroad need to be considered after discussing with EPI.

In case of death suspected to be due to an AEFI, an autopsy needs to be performed as soon as possible (within 72 hours) to avoid tissue lysis (for e.g. in the adrenal glands), which can alter diagnosis. Samples for both toxicology and pathological examination should be sent to the reference laboratories identified by EPI as early as possible to avoid loss of biological samples due to decomposition. It is essential to ensure that a detailed patient's history is included in the autopsy form and submitted to the autopsy team to help them look for any underlying pathologies.

6.1.1. Guide to human specimen sample collection

The details of the type of AEFI, the tests to be performed, the specimens to be collected, the process of storage and shipment and the labs are outlined in Table 6.1

Table 6.1 Type of AEFI, the tests to be performed, the specimens to be collected, storage and shipment procedures and the labs conducting tests

Suspected AEFI	Diagnostic Method	Specimen	When to collect	Preparation, Storage and shipment	Referral laboratory for Specimens
Injection site abscesses	Microscopy and Culture/ sensitivity	Pus Swab	At contact	Use transport media to transport Pus swabs to the next level	**EPHI** or other accredited laboratory
BCG lymphadenitis	Microscopy, Culture and serology	Blood, LN Aspirate or Biopsy and Suspected Vial Batch	At Contact	Wrap in leak proof and water proof container transport. Vaccine sample should be transported in reverse cold chain	**EPHI** or other accredited laboratory
Collapse or shock-like state	Microscopy, Culture and serology	Blood and Suspected Vial Batch	At Contact	• Blood smear • Blood sugar tests at site • Ensure asepsis for blood collection for culture	**EPHI** or other accredited laboratory
Convulsions or Seizures	Microscopy, Culture and antigen detection	Collect CSF from affected cases	At Contact	• Ensure aseptic techniques of lumbar puncture • Never use vials that contained antibiotics • Sugar and cell counts should be done at site • Transport to referral laboratory immediately	**EPHI** or other accredited laboratory
Encephalitis	Microscopy, Culture and antigen detection	Collect CSF from affected cases	At Contact	• Ensure aseptic techniques of LP • Never use vials that contained antibiotics • Sugar and cell counts should be done at site Transport to referral laboratory immediately	**EPHI** or other accredited laboratory
Death	Serology	• Venous Blood • Vial Batch	Immediate	• Never use vials that contained antibiotics • Transport to referral laboratory immediately • Transport sampled vial batch in reverse cold chain	**EPHI** or other accredited laboratory

6.2. Vaccines and logistics

Vaccines and logistics samples from the site and the distribution point(s) should be collected as soon as possible and kept in cold chain. They should be sent to the selected laboratory for testing only on the recommendation of National AEFI Committee.

Testing of vaccines and logistics should be requested on a clear suspicion and not as routine and never before the working hypothesis has been formulated (Table 6.2). Determining which samples to send for testing (if any) depends on the working hypothesis for the cause of the event(s). If the used vial of suspected vaccine is available, it should be separately labeled and sent along with unused vials of the same lot.

The regulatory body for the concerned woreda will be responsible for the packaging, cold chain maintenance and shipment of samples in the correct temperature to the national laboratory at EFMHACA. ALL specimens sent to the lab should be accompanied by a laboratory request form (Annex4).

N.B. The expenses related to sample collection and, transportationshould be obtained from EFMHACA.

The laboratory will process the specimens and send the laboratory results to EPITeam Leaderand EFMHACA Pharmacovigilance Team Leader. Laboratories will also send a copy of the laboratory results to all persons with contact details (complete address with postal code, phone and fax numbers and email address) mentioned in the lab request form

Table6.2 Laboratorytestingto investigate AEFI by working hypothesis

Workinghypothesis	Specimenstosend	Laboratorytest
Vaccine transportation or storage	Vaccine vial	Visual test for clarity, presence of foreign matter, turbulence, discoloration or flocculation (examine under magnification)
Reconstitution error	Vaccine vial and/or diluents	Chemical composition analysis for abnormal components (e.g. suspect drug used instead of vaccine or diluent), or microbiological culture for bacterial contamination
Non-sterile injection	Needle, syringe, vaccine vial and diluents	Sterility, if an infectious cause is suspected
Vaccine problem	Vaccine vial	Chemical composition analysis: preservatives, adjuvant level, etc. (e.g. aluminium content) or biological tests for foreign substances or toxins if abnormal toxicity is suspected

7. Analysis of AEFI data

Immunization and AEFI surveillance should include structured, systematic and permanent data collection on the impact of vaccines used in the country immunization program. In order to measure this effect, epidemiological analysis of data is required as well as dissemination of findings to advice program managers, and other stakeholders including manufacturers.

Analysis of data on AEFIs consists of reviewing the case investigation report for each client, reviewing other data about the event (such as immunization practices 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, managers 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).

Analysis of data on AEFI is contingent on the following components:

- Reporting of AEFI by health and vaccine providers and consumers
- Completeness of submitted AEFI forms or the reports.
- Verification and reassurance of data accuracy.
- Identifying health institutions where AEFI are not reported. Determination of whether it is due to failure of reporting or whether there are no AEFI to be reported. Checking on “zero reporting” or “nil reporting”.
- Analysis of AEFI reports and performance of causality assessment to classify the AEFI’s.
- Assessing number of AEFI’s and rate for 1000 or 10 000 or 100 000 doses of vaccine used over a stipulated time period.
- Assessing number of cause specific AEFI’s and rate for 1000 or 10 000 or 100 000 doses of vaccine used over a stipulated time period · Comparison of these observable rates with available or expected known events either vaccine reaction and/or background rates.

7.1. Who should analyze the data?

Data analysis could be carried out at different levels in the AEFI surveillance system: program implementation level, regional level and national level. The extent and purposes of analysis will vary by different level. The analysis that is repetitive at different levels may necessarily vary by the extent of the analysis. Analysis of data at immunization service provider level is very important to identify the immunization errors. This is largely to carry out corrective action in a timely manner.

7.2. How should the data be analyzed and interpreted?

Step 1: All reported AEFI data need to be line listed. Line listing will help for initial identification of clustering or any unusual or significant reporting events that need further analysis.

Step 2: Tabulating AEFI data by place, person, time, antigens and type of events (high fever, abscess). 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 abscess by one immunization centre is more likely due to immunization error.) However, further investigation of such observation is necessary to confirm 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 5.1: 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)

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%

Multiplier: Use of proper multiplier is important as it must 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 2.5 and2.6 in Section 2) present a guide to making 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. 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).

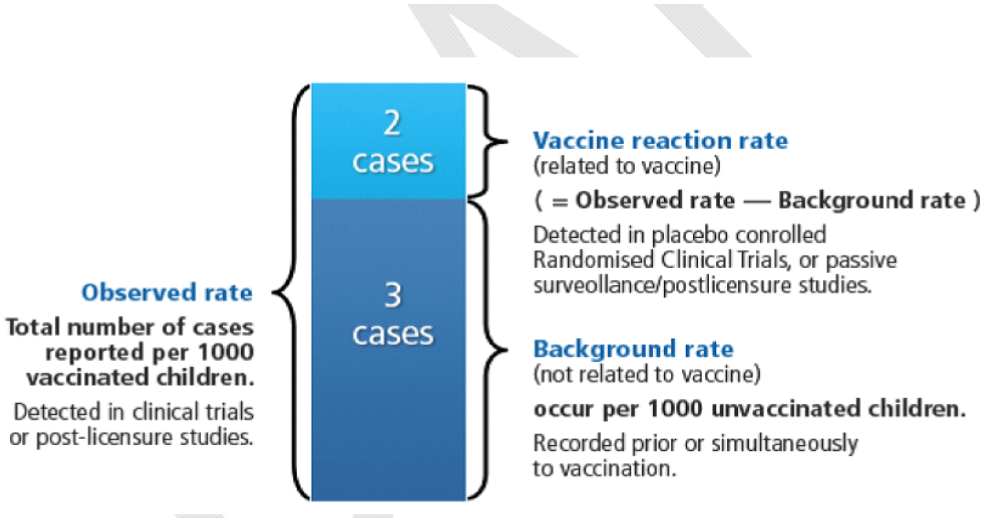


Figure 6.1: Vaccine reaction rate, Observed rate and Background rate

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'. For example, the DTaP vaccine given as a primary dose is less likely to result in extensive limb swelling when compared with the same vaccine given as a booster dose.

Case definition Adverse 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 (www. brightoncollaboration.org). Ethiopia will use this standardized definition.
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.

7.3. How should a cause be determined?

Until the investigation is complete a working hypothesis is all that can be formulated. Later it will be possible to analyze 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 an 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.

Table 7.2: Purpose of data analysis at different level

Program implementation level	What data to analyze	Purpose of data analysis at given level
Local level (Immunization provision level)	Number of reports by clinics, hospitals, villages by a given time Reported AEFI by place (clinics, hospitals), persons and time Reported AEFI by antigen	These are program operation/surveillance performance indicators (timeliness, completeness). Identification of immunization related errors will lead to corrective action. Will identify vaccine reactions and coincidence.
Sub national level (Regional/ zone/ woreda)	Number of reports by locallevels Reported AEFI by place (clinics, hospitals), persons and time Cluster analysis Reported AEFI by antigen	These are program operation /surveillance performance indicators (timeliness, completeness) at local level. Identification of immunization related errors will lead to corrective action. Cluster analysis leads to identify immunization related errors, coincidence and vaccine reactions. Will identify vaccine reactions and Coincidence.
National level	Number of reports by intermediate levels Reported AEFI by place (clinics, hospitals), persons and time Cluster analysis Reported AEFI by antigen	These are program operation /surveillance performance indicators (timeliness, completeness) at intermediate level. Cluster analysis leads to identify immunization related errors, coincidence and vaccine reactions. Will identify vaccine reactions, including signals detection. Leads to taking operational and policy decisions in the country.

7.3 Monitoring and Evaluating the performance of the AEFI surveillance system

The AEFI surveillance system performance needs to be regularly reviewed at all levels to ensure that the system is sensitive enough to identify and respond to AEFI rapidly. The "standard overall" indicator proposed to determine the quality of AEFI surveillance is, " AEFI reporting ratio in surviving infants from a sub-national1 area/country per year". This is calculated as

$$\text{AEFI reporting ratio per 100,000 surviving infants per year} = \frac{\text{Number of AEFI cases reported from a sub-national area/ country per year}}{\text{Total number of surviving infants in the same sub-national area/ country per year}} \text{ X } 100{,}000$$

Notes: The target proposed is at least 10 reports per 100,000 surviving infants per year. The sub-national area/country is defined according to the functional requirements and setup of the national AEFI surveillance system.

Some of the other key indicators that help to monitor the performance of the system include

- Timeliness and completeness of AEFI reporting
    - Percentage of AEFI cases reported on time (< 24 hours of notification) to the national level
    - Percentage of serious AEFI cases investigated on time (< 48 hours of onset) using standard formats.
- Number (%) of AEFI investigation conclusions supported by findings of special tests (clinical specimens, Post-mortem findings (among AEFI deaths), lab findings for vaccine samples)
- Number (%) AEFI cases where final classification including causality assessment by AEFI committee is completed within 30 days of receipt of all documentation from districts
- Number (%) AEFI cases reviewed by National AEFI committee following receipt of reported AEFI cases from region at National level.
- Number (%) AEFI cases reviewed by National AEFI committee and not assessable due to lack of information.
- Response to AEFI by the program particularly those related to programme error

[1]It is assumed that a country could have three levels of immunization safety surveillance: national (central), Subnational or intermediate (state/province/region/district) and service-provider level

4An estimate of **Surviving Infants** can be calculated by subtracting the number of children who die before they reach their first birthday from the number of children born during that year.Number of children dying during the first year of their life can be estimated by dividing the number of births by 1000 times the infant mortality rate (IMR), where the infant mortality rate is expressed as number of infant deaths per 1000 live births.

8. Brief overview of AEFI causality assessment

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 program and regulation of the safety and quality of the product. Vaccine recipients want to know whether what they have experienced was due to the vaccine. They may believe that because one event followed another, it was causal. It can be difficult to explain that 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 vaccine. 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.

Table 8.1: Advance and limitations of standardized causality assessment

What causality assessment can do	What causality assessment cannot do
Classify relationship likelihood	Change uncertainty to certainty
Prove the connection between drug and event	
Decrease disagreement between case assessors	Give accurate/quantitative measurement of relationship likelihood
Improve scientific evaluation of cases; education	Quantify the contribution of a vaccine to the development of the adverse event
Mark individual case reports	Distinguish valid from invalid cases

The quality of the causality assessment depends on three factors:

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

With inadequate or incomplete case information, an adequate causality assessment might not be performed or the AEFI may be deemed unclassifiable or non-assessable due to lack of information. On the other hand, even with complete information the AEFI may be indeterminate due to lack ofclear evidence of a causal link or conflicting external evidence or other inconsistencies. Nevertheless, these determinations should be recorded because the reporting of more cases may lead to a stronger signal and a plausible hypothesis, or stronger refutation of any link.

In summary, causality assessment usually will not prove or disprove an association between an event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

8.1. Levels of AEFI causality assessment

While causality assessment of AEFI applies to investigating relationships between a vaccine and an adverse event at three levels (the population level, to test if there is a causal association between the usage of a vaccine and a particular AEFI; at the level of the individual AEFI case report, to determine from evidence and case assessment if an AEFI in a specific individual is causally related to the usage of the vaccine; and third in the context of the investigation of signals by assessment of a series of case reports), they all depend at some level on performing an assessment for causality of individual cases.

- **Individual AEFI case report:** In order to estimate the probability that the occurrence of a reported AEFI in a specific individual is causally related to the usage of the vaccine. 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: individual AEFI cases, surveillance data and, where applicable, cluster investigations as well as nonclinical data.

The scientific basis for the assessed criteria in the process includes the following:

Temporal relationship: The vaccine exposure must precede the event occurrence. Exposure always precedes the outcome. If factor "A" is believed to cause a disease, then it is clear that factor "A" must always precede the occurrence of the disease. This is the only absolutely essential criterion.
Definitive proof that the vaccine caused the event: Clinical or laboratory proof that the vaccine caused the event.
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: This is defined by the size of the association as measured by appropriate statistical tests. The stronger the association, the more likely it is that the relation of "A" to "B" is causal.
Consistency of the association: The association is consistent when results are replicated in studies in different settings using different methods. That is, if a relationship is causal, we would expect to find it consistently in different studies and among different populations. This is why numerous experiments have to be done before meaningful statements can be made about the causal relationship between two or more factors.
Consideration of alternate explanations: In doing causality assessment, all reasonable alternative etiologic explanations need to be considered.
Prior evidence that the vaccine in question could cause a similar event:
The concept of 're-challenge' which is more commonly used in drug causality, but has also been helpful for certain vaccine-event considerations (for example, Gullian-Barre Syndrome or GBS

occurring on three separate occasions in the same individual within weeks of administration of tetanus vaccine).

8.2. Case selection for causality assessment

Not all AEFI incidents that are reported, even if investigated in detail, need to have a formal causality assessment performed. In some cases, it becomes immediately clear that symptoms onset before the vaccination. Generally, it is recommended that causality assessment be done for the following:

- Serious AEFI, as per the regulatory definition of serious (i.e. events which are life-threatening or leading to death, hospitalization, significant disability or congenital anomaly), where it is important to evaluate whether a vaccine could have been responsible for the event.
- Clusters of events above an expected rate or level of severity, where it is important to establish whether the number of cases related to vaccination is truly elevated and thus action needs to be taken.
- Signals generated as a result of an unusual individual case or a cluster cases that then will warrant further analysis other investigation.

Other AEFI as outlined below if there is a need to assess them in more detail given their potential need for a detailed investigation or follow up:

- AEFI that may have been caused by immunization error, (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome),
- Significant events of unexplained cause occurring within 30 days after a vaccination (and not 1 listed in product label), and
- Events that are causing significant parental or community concern and where a formal case assessment can provide a detailed, more reassuring explanation to the parents and/or community (e.g. HHE, febrile seizures).

8.3. Preparation for AEFI causality assessment

There are three prerequisites that every AEFI report should fulfill before causality assessmentis going to be conducted:

- 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. They should include documents pertaining to the investigation as well as laboratory and autopsy findings as appropriate.
- There must be a “diagnosis” (see below) for the adverse event, clinical sign, abnormal laboratory finding, symptom and/or disease in question. In other words, the event being assessed should be clear – it should be understood both which vaccine is being associated with what specific event that was reported.

8.4. Causality assessment team

Causality assessment in Ethiopia is done by the National AEFI Committee that is:

- Independent
- Free of real or perceived government, industry conflicts of interest
- Has broad range of expertise in the areas of 'infectious diseases, paediatrics, epidemiology, microbiology, pathology, immunology, neurology and vaccine program.

The committee has written terms of reference (ToR)

In summary, causality assessment of serious cases needs high levels of expertise and will be done by National AEFI committee only. An assessment usually will not prove or disprove an association between an adverse event and the immunization. It is meant to assist in determining the level of certainty of such an association. A definite causal association or absence of association often cannot be established for an individual event.

8.5. Causality assessment method

Determining causality of AEFI, particularly those considered severe, of public importance, and programmatically disruptive are critical for ensuring vaccine safety. In 2012, WHO developed a method to assist the national committees for AEFI case review and causality assessment. A repository of all AEFI cases evaluated through the new method is considered critical and would facilitate signal detection in future. It will also determine the need for additional epidemiological studies. Cases considered incomplete are directed towards additional case investigation and review. This was harmonized after the Clinical Immunization Safety Assessment (CISA) Network developed new algorithm and CIOM proposed the new definitions of AEFI.

The revised process envisages the causality assessment of an individual AEFI case to a particular vaccine. In the event of multiple vaccines being given simultaneously, the assessor will have to conduct a causality assessment separately for each suspected vaccine. 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 I).

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

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

Step 1: Eligibility

This may be self-evident, but to proceed with causality assessment, it is necessary to first confirm that the vaccine was administered before the event occurred. This can be ascertained by eliciting a careful history with the relevant stakeholders to ascertain the timing of vaccination with the onset of any signs and/or symptoms related to the event being assessed. It is also essential to be clear on the "diagnosis" of the reported AEFI. The valid diagnosis could be a clinical sign, symptom, abnormal laboratory finding, or disease with clear details as to onset. The diagnosis should also meet a standard case

definition for the disease process being assessed. If available, it is best to adopt one of the Brighton Collaboration case definitions (see References). However, if this is not possible, case definitions can be adapted from the standard medical literature, national guidelines or local clinical practice. If the reported event does not have a valid diagnosis, it may not be possible to adequately categorize the AEFI and additional information should be collected to arrive at a valid diagnosis or clear definition of what event is being assessed for causality against the given vaccination. 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.

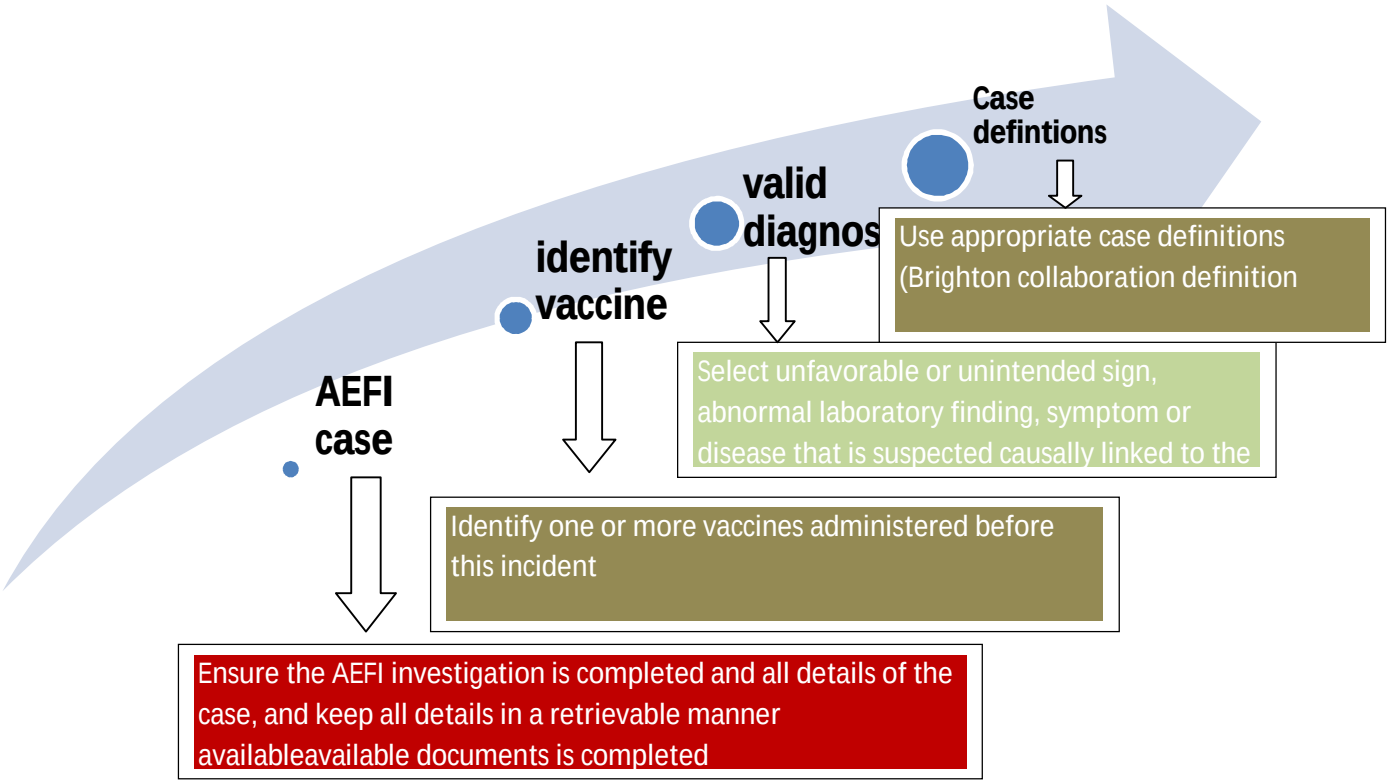


Figure 8.1: Eligibility of causality assessment

It is important that, if an AEFI is reported and appears to not meet the eligibilitycriteria because of suspected 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 reviewers/investigators should define the "causality question" as here below

Has the_____vaccine/vaccination caused_____?

Step 2: checklist

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

- Is there strong evidence for other causes?
- Is there a known association with the vaccine / vaccination?
    - vaccine products
    - immunization error
    - immunization anxiety

If the response to any question under 2 is "yes", then it is necessary to ask: "Did the event occur within an appropriate time window after vaccine administration?"

- Is there any strong evidence against a causal association?
- Other qualifying factors for classification: background rate of the event, present and past health condition, potential risk factors, medication, biological plausibility, etc.

Once the checklist (Annex 2) is systematically completed, the answers in the checklist are applied to the algorithm.

Step 3 Algorithm

The algorithm follows the key questions and related answers on the checklist. A stepwise approach using the algorithm helps determine if the AEFI could be consistent or is inconsistent with an association to immunization, is indeterminate or is unclassifiable.

A detailed description of the algorithm and how to make use of it is in the User Manual referenced underneath and linked in the Reference list. In particular, some of the responses such as to IA, IIA and IIIA have greater strength and these conclusions have greater weight. When the conclusion is "unclassifiable", the reviewers should determine the reasons why classification was not possible and all attempts should be made to obtain the necessary missing information or evidence needed to allow for a classification.

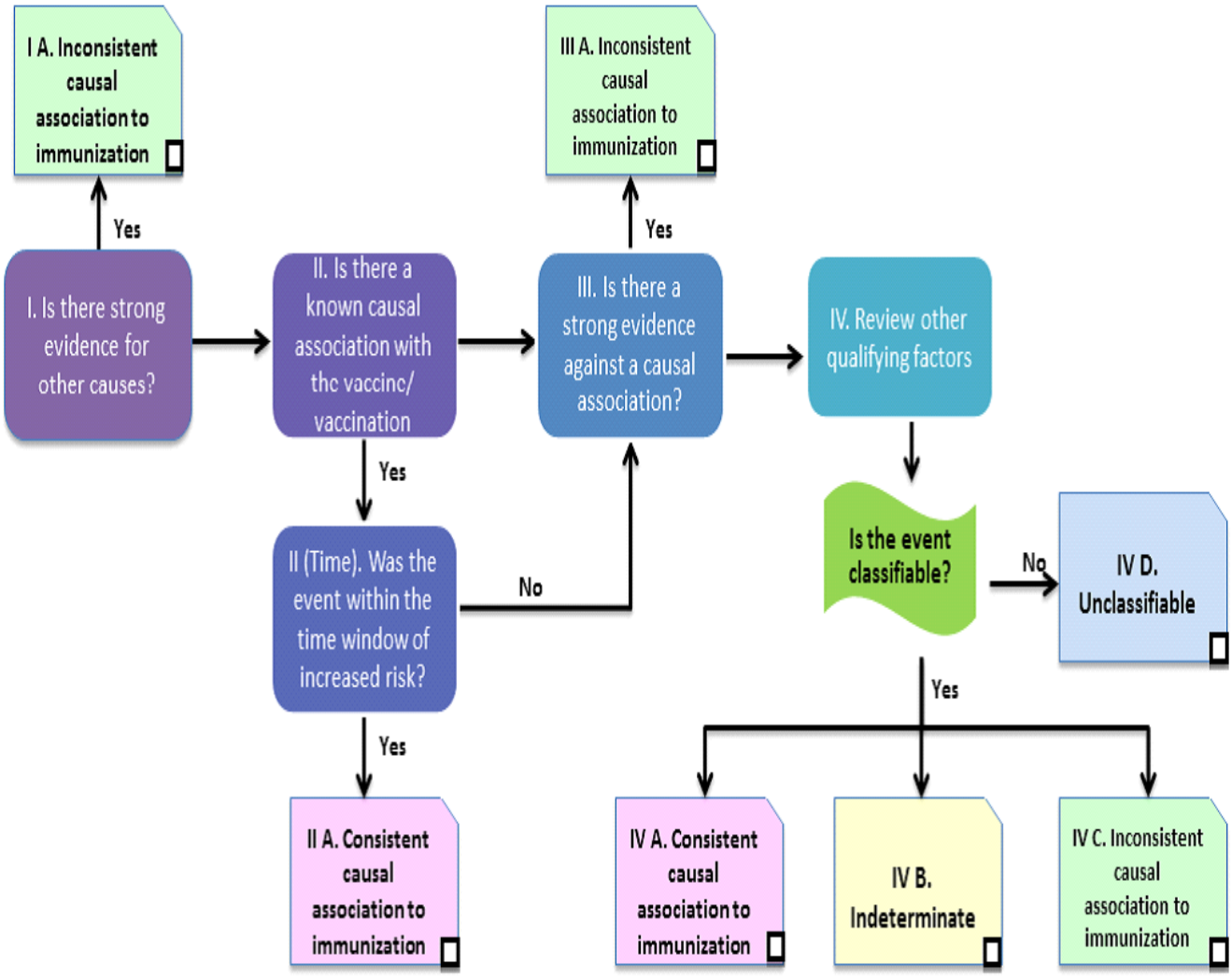


Figure 8.2: Causality assessment algorithm

Step 4: Classification

The final classification is based on the availability of adequate information. It is for the benefit of the final classification that all relevant information should be collected ahead of time during the investigation

I. A Case with adequate information for causality conclusion can be

Classified as follows:

A. Consistent causal association to immunization

A1: vaccine product- related reaction or A2: vaccine quality defect-related reaction orA3: immunization error-related reaction or A4: immunization anxiety-related reaction.

B. Indeterminate

B1. Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing the event (may be new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.

B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization.

C. Inconsistent causal association to immunization (coincidental)

C1. Underlying or emerging condition(s), or

C2. Conditions caused by exposure to something other than vaccine.

II. A case without adequate information for causality conclusion is

"Unclassifiable" and requires additional information for further review of the causality.

This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine. A case without adequate information for causality conclusion is "unclassifiable" and requires additional information for further review of the causality. The available information on unclassifiable cases should be placed in a repository or an electronic database which should be periodically reviewed to see if additional information is available for classification and to perform analyses for identifying signals.

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

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

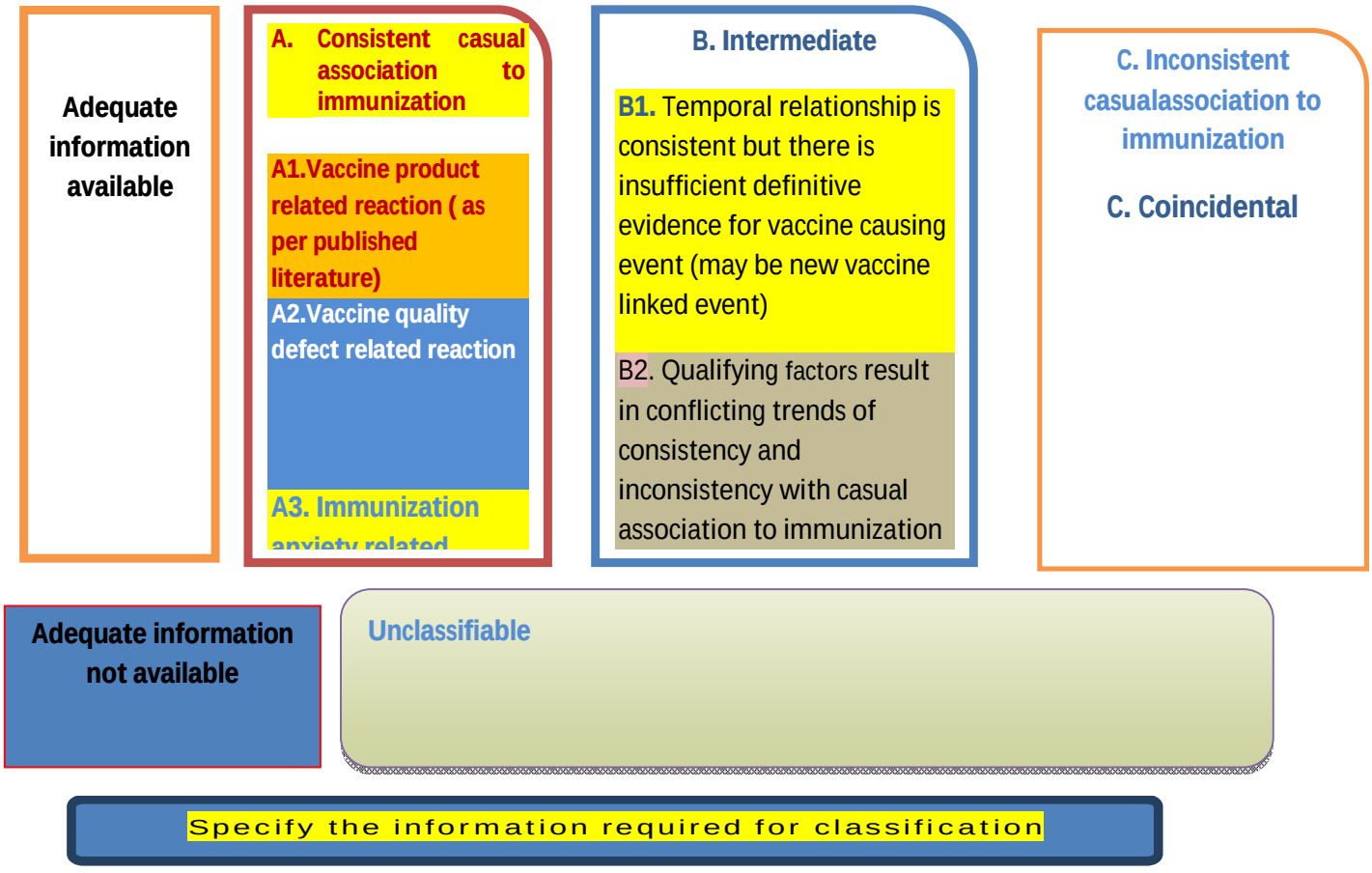


Figure 8.3: Causality assessment classification

8.6. What actions can be taken after causality assessment?

The most important in causality assessment is the action that is going to be taken after the outcome of causality assessment. 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 recallof the vaccine and so on – to avoid and/or minimize recurrences.

Based on global guidelines, EFMHACA and the EPI programs have proposed the following actions for responding to AEFI. The following section provides some examples of the types of responses to take to the different causality conclusions resulting from the assessment:

A. Consistent causal association to immunization

A1. Vaccine product-related reaction (Figure 8.3)

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 EFMHACA and global partners such as WHO and UNICEF.

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

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.

C. Inconsistent causal association to immunization (coincidental)

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

Corrective actions

Considering the situation or event, responding to AEFI may be immediate short-term activities or/and long-term follow- up activities depending on the occurred events stakeholders readiness to implement. 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 impact on national immunization program as well as on regional, zonal and woreda programs and planning.

Patient care

Treatment must be the first response to an AEFI. Mild symptoms such as mild fever and pain are likely to be of short duration and can be managed by assuring and educating parents during immunization. Health workers need to know how to recognize, treat, and report AEFI immediately, if serious. It is of utmost importance to ensure that proper and early treatment is received by affected vaccinees (patients). The treatment of vaccine reactions (e.g. fever, pain, tenderness and swelling) depends on the type of reaction and treatment principle is similar to other symptoms.The vaccinating health facility should provide all possible supports in management of the case including arrangement of referral to higher level, if needed.

Investigation

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. It is never appropriate to discontinue the immunization program while awaiting the completion of the investigation.

Table 8.2: What actions can be taken during investigation?

Phase of investigation	*Actions*
Incident detected	• Assess and investigate with appropriate degree of urgency • Start communication with all concerned parties
During investigation	• Ensure that investigator has adequate resources, provide more if needed • Increase surveillance to identify similar cases in and out of area: • Sometime it requires enhanced or active surveillance to gather more information/data • Define any suspect vaccine. • Keep continue communication with all concerned parties on process of investigation without suggesting the cause

Phase of investigation	*Actions*
Investigator develops working hypothesis	• Don't communicate working hypothesis until confirmed(it is only for investigating team) • If program related errors are working hypothesis, correct them • Vaccine problems suspected, quarantine suspect vaccines
Investigators confirms working hypothesis	• Advise community of cause, and of planned response • Communication with all concern parties on findings

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 is not clear.

Logistics

Immunization supply chain, injection safety and waste management are part of AEFI surveillance. It is highly recommended to improve supply chain system and ensure safe injection practices. The EPIprogram of the FMOH, PFSA and EFMHACA 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.

8.7. Action and response to AEFI

Responding to AEFI may involve 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 team/AEFIcommittee.

Proper and early treatment should be provided to patients regardless of the diagnosis. Case management and referral will vary depending on the seriousness. 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. If parents return to seek medical attention, these cases should be documented and reported in the AEFI case reporting form (Annex 1). In case patients need hospitalization, a clear system for referral should be in place.

Table 8.1 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, EFMHACA 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 workers; • 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.

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. 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.

9. Communication and media management

9.1. Risk communication

Communication makes stakeholders aware of the process at each stage of the Investigation. The identification of particular interest groups and their representatives should comprise a part of an overall communication strategy. Decisions including what, whom and how, should be part of an overall communication strategy.

The first issue to be discussed as a program manager is whether or not to communicate this information, how the information should be communicated, and also to whom this should be addressed. Above all, it is very important to understand the nature of AEFI and also whether real or perceived, because any AEFI can become a crisis situation if it is not handled correctly and wisely.Informing the public appropriately may boost confidence in the immunization system,

The need for proactive communication increases as the potential impact on the vaccination program, and public trust in the program, increases. In a situation with an anticipated low impact, the need to communicate is limited. In a situation with an anticipated high impact, the need is more pressing. When judging the potential impact of an AEFI, the main criterion is *whether the event will attract public attention and thus affect the public's trust in the vaccine program*.

Regardless of the AEFI, the first step is to identify what has happened. This information is key to understand whether the event has a low, medium or high impact. Two principles extend across the advice below.

- If in doubt, communicate. From a public trust standpoint, it is far better to be on the side of too much communication, than too little.
- Do not delay in deciding and implementing your communication strategy. Events unfold quickly and the situation can change.

Be flexible and ready to take action if events that initially seem to have low impact on the vaccine program suddenly escalate to high impact. (Selecting your response to a vaccine-related event) outlines when an event may be considered low, medium or high risk to public health and/or the immunization program. This categorization of the event enables you to determine the most appropriate response. In general, low-impact events will not require a response, but medium and high impact ones will.

Need for improved communication

Concerns are frequently raised about vaccines and immunization programs by members of the general public and in the media. These concerns can be serious and are often misplaced. The graphic below (Fig 9.1) illustrates some of the factors that may trigger public concerns; hence, the need for improved quantity, quality and targeted communication about vaccine safety.

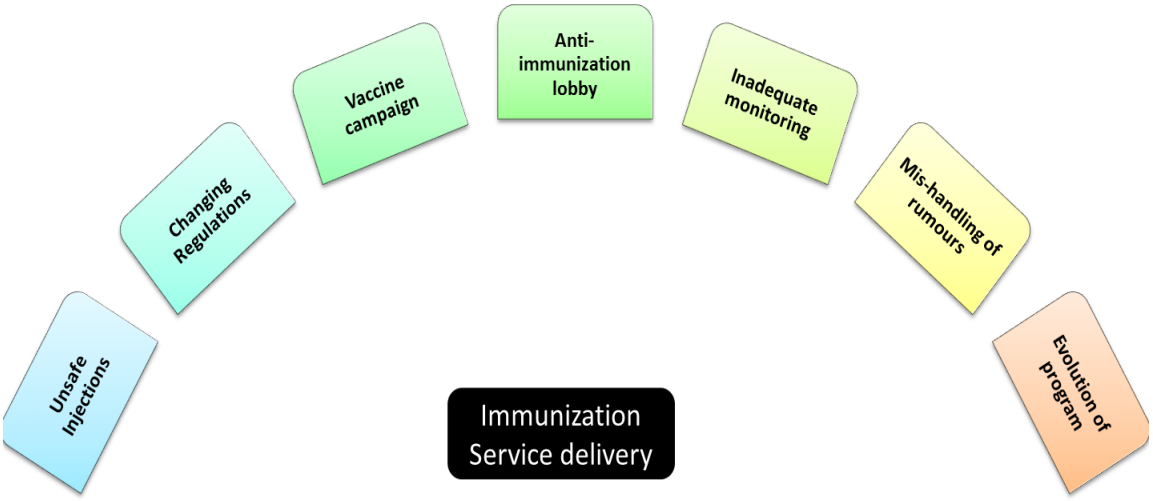


Fig 9.1 Factors triggering public concerns to immunization

Challenges to effective communication

Challenges that need to overcome with effective communication include among others:

- Communicating the decline of childhood infections and deaths from VPD
- Parents view that infectious disease is a thing of the past
- Introduction of new vaccines and related information gaps
- Vaccination Campaigns or Supplemental Immunization Activities (SIAs)
- Need for transparency and accountability

9.2. Communication with clients, parents or guardian and community

Communication with parents, other members of the community, health staff and media need to be carried out under all circumstances. They should be kept informed about the investigation, results and action taken already or going to be taken regarding the AEFI. It is crucial to highlight the benefits of immunization while communicating on AEFI with the public and stakeholders.

Key points to consider when communicating with the vaccine recipient (patient or client) or parents and guardians of the patient, community and health staff are;

- Listen to the client, parents or guardian and their concerns empathetically.
- Reassure and support the client, parent or guardian but do not make false promises.
- Assist the client, parents and guardian for hospitalization if necessary.
- Frequent communication with the client, parents or guardian regarding the progress of the patient.
- Prepare a fact sheet on adverse event for the client, parents or guardian, community, health staff and media.
- Build up and maintain relationship among health staff, community and media.
- Inform the individual client, parent or guardian about possible common adverse events and how to handle them.
- Continuously communicate with the client, parent or guardian and community during the investigation period to assure understanding the risk-benefit of vaccination.

9.3. Role of health care worker in community communication on AEFI

AEFI can have repercussions on the entire routine immunization program as well as campaigns. Where medical interventions are necessary, they should be carried out as rapidly as possible. Suppressing reports of AEFI or slow reaction can cause considerable damage to the immunization program in the long-term. Messages relating to adverse events must be disseminated rapidly to prevent rumors spreading.

Once an AEFI has occurred, responses should include the following communication elements:

- Communicate immediately with the higher level in the EPI and EFMHACA
- Provide the parents with factual information. Remember that some parents may seek information elsewhere and you may lose credibility if you do not provide a trustworthy and technically sound response. The public and the other stakeholders have a right to know exactly what happened.
- Reassure parents, caregivers and adults that necessary measures are being taken so that the members of the community and caregivers are informed of what is happening.
- Communicate the results of the investigation to the program managers and to the EPI officers at all levels.
- If the AEFI was caused by immunization error, tell the parentswhat steps are being taken to prevent similar events in the future.
- Repeat the message to dispel all fears.
- Constantly reassure the public of the safety of vaccines.

9.4. Communication with other healthcare staff

- Communicate among all level of health authorities involved.
- Reinforce their knowledge, ability, skills and performances.
- Update them on investigation process, progress and findings.
- Reassure the staff of ongoing confidence in the immunization program; quality of the vaccine and their services provided
- Do not blame health care worker, instead focus on the correction and quality of the EPI program.

9.5. Communicating with stakeholders

Vaccine safety information needs to be shared with other stakeholders in order to ensure dissemination of correct information and thereby ensuring the smooth functioning of EPI program. Depending on the need stakeholders mentioned below will be given preliminary information at initial stage and final report after completion of investigation and causality assessment at a later stage.

- EFMHACA
- PFSA
- EPHI
- National AEFI Committee
- AEFI task forces at regional levels
- Policy Makers and other government authorities
- Professional associations
- Universities and health facilities
- International agencies and development partners
- Manufacturers

9.6. Communicating with 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 vaccinationcampaigns. 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.

Advance preparedness

Effective communication with the media includes efficient coordination with the field staff, a plan, trained personnel, budget and practiced responses to potential issues around AEFI. Effective communication should be in place before an immunization campaign starts and as part of the on-going communication to support routine immunization programs.

A database of journalists

It is essential to maintain a database of print and electronic media journalists covering health (local, national, international) with contact information. They need to be contacted and informed about the circumstances of the AEFI.

Information packages

Keep media informed through email or hardcopy by sending regular updates on any plans, programs and decisions. Sensitize media about health benefits of immunization and its impact globally and nationally. Prepare monthly or quarterly updates. Provide an updated information package with documents including Frequently Asked Questions (FAQs) on immunization in general, for specific disease and AEFI (Factsheet or a technical brief on a specific vaccine preventable disease etc.).

Draft media release

The draft media release must specifically answer the 7W's for journalists:

- Who is affected?
- What has happened?
- What is being done?
- Where has it happened?
- When did it happen?
- Why did it happen?
- Will it happen again?

In the media release, mention the name and contact details of the AEFI focal person(s) and the name and contact details of the official spokesperson for further details should journalists have additional questions (at the end).

A spokesperson system

The regionallevel shall be the first authority in releasing the information to the media. For this purpose the RHB Public Relations Officer shall be responsible for communicating the AEFI to media, public and stakeholders. This limits the possibility of conflicting messages coming from different sources. The Regional EPI Officer should ensure that the spokesperson has the important information.

Orientation workshops and field visits for media:

Regular orientation workshops and field visits for journalists will help them achieve a better understanding of immunization advantages as well as the complexities of an immunization programme. This will also help to identify in advance the kind of questions or concerns that journalists specifically have.

Media Management during an AEFI crisis

While every single AEFI must be investigated in detail, all AEFI cases may not be a crisis situation. A crisis often occurs from inaction rather than from taking appropriate action on AEFI. The following activities should be implemented.

a. Monitoring of media

When an AEFI occurs, media should be monitored for authenticity of their reporting. The EPI and EFMHACA communication teamsshould move very quickly to correct any inaccuracies. These communication teamscould take the following immediate actions:

- Analyze rumor, its level and potential to cause damage.
- Anticipate how situations might evolve following response; prepare before responding.
- Deal with a simple mistake in reporting with a simple solution. If it is an isolated error, make a polite call to the reporter and offer to help the reporter with correct data and facts then and in the future.
- If the rumor is confined to a small audience, correct it within that group only. If the error is widely reported, it may be necessary to call a media conference to present the correct facts before it leads to further damage.
- Plan how to prevent future rumours.

b. Prepare a media release

An effective media release should include a complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI or coincidental event). This media release should be prepared by the national Public Relations Officer based on the information provided by the EPI, EFMHACA and National AEFI Committee. The media release should have;

- An outline of actions taken or planned (such as the AEFI investigation).
- A description of the cause of the event (but only when this is known with certainty).
- An assurance that corrective action has been taken or will be taken.
- Reference to any relevant publication, video material or web site.
- Sender’s name and spokesperson’s details.
- Limited to one page of matter (400-500 words max).
- Short sentences (not exceeding two lines).

Quotes from key officials may be used after seeking their permission. The quotes must be positive and carry the key messages. The media release can be provided more than once depending on the progress of the situation.

c. Call a media conference

Media conferences may need to be conducted if AEFI is being reported extensively and widely and there is a need to provide accurate facts and de-sensationalize the story. A media conference enables all journalists to have the same information, thus there is then less likely of event being 'sensationalized'. Consider the following steps when preparing for the media conference:

- The FMoH Public Relations Office takes the lead but identifies who facilitates the press conference.
- If there are several members on the panel, agree beforehand on the key message(s) in response to the AEFI.
- Agree on roles of each panel member beforehand, including the type of questions (media, political etc.) each panel member may best handle.
- Panel members must avoid contradicting each other in the press conference unless it is critical to clarify something incorrect that has been said.
- Have a media kit ready and share it with journalists. The media kit may consist of a media release with all the essential information, supplementary background information, benefits and a set of frequently asked questions about immunization.

9.7. Media Management post AEFI

Keeping promises to the media

If it has been promised that media will be kept updated about the investigation findings, make sure the media is updated by the promised date. If the findings have been delayed, ensure the media is informed because they would be expecting answers.

Providing answers to unanswered questions

During media conferences, if a question could not be answered for any reason – for example due to absence of data or if you were unprepared to answer the questions – get back to the media with the answers as soon as possible.

Keeping media informed about subsequent developments

If any decision or action is taken at the highest levels following AEFI investigations or during the investigations and the public must know about it, keep the media informed through a press release or hard copy document. The FMOH website www.moh.gov.etand the EFMHACA website www.fmhaca.gov.et can be used as an excellent interface to update the media.

9.8. Dealing with rumours and misinformation

In the context of immunization, rumour is defined as an unverifiable assertion that is circulating, or a statement without facts to confirm its truth. Rumours and misinformation about immunization are amongst the most serious threats to the success of any immunization program. Once rumours start they can be very hard to stop.

Some examples of rumours:

- "Vaccines are a contraceptive to control population or to limit the size of a certain ethnic group."
- "Vaccines can lead to infertility in girls."
- "Vaccines are contaminated by the AIDS virus."
- "Children are dying after receiving vaccines."

Unless the rumour can very easily be contained and addressed you must refer the matter to your supervisors **as quickly as possible**. You will need to work under their direction - action may even need to be taken at the national level. The consequences of rumours can be serious and, if unchecked, they can spreadquickly beyond your local area.

Common causes of Rumours

- Inadequate information sharing by health care providers or
- Failure to communicate correct information about vaccine effects and schedules,
- Failure to check whether caregivers know and understand information,
- Failure to give clients opportunities to ask questions
- Parents/caregivers' negative attitudes about immunization services
- Delayed or no response to an AEFI

• *What you can do at the health facility*

The WEO with support from healthcare workers can:

- Meet with key opinion leaders (politicians, traditional and religious leaders, community leaders, other health workers).
- Organize meetings at sites where the individuals/groups are comfortable and feel at ease to ask questions.
- If there is a national mass media response, encourage your community members to watch and talk about it.

• *Words of advice*

- React swiftly and adapt your ongoing activities to give a quick response.
- Develop strong relationships and trust with your community in advance (religious, social and media groups).
- Give clear and consistent messages.

Annex 1: ETHIOPIA AEFI CASE REPORTING FORM

REPORTING FORM FOR ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI) (to be filled by the Healthcare Worker)

AEFI Reporting ID Number _____

***Patient's Full name*:** _____ ***Patient's full Address*: Got/Village_____ Kebele_____** **Woreda_____Zone____ Region_____** **Medical Record/Card No.----------** **EPI Registration Number**_____ Telephone: Sex: ☐M ☐ F ***Date of birth (DD/MM/YYYY)*:** _ _/_ _/_ _ _ _ *OR Age at onset :* ☐☐*Years* ☐☐ *Months* ☐☐☐ *Days* *OR Age Group:* ☐*< 1 Year* ☐ *1 to 5 Years* ☐*> 5 Years*	***Reporter's Name*:** Institution : Designation &Department: Address: Telephone & e-mail: Date patient notified event to health system (DD/MM/YYYY): _ _/_ _/_ _ _ _ Today's date (DD/MM/YYYY):_ _/_ _/_ _ _ _

Health facility (or vaccination center) name:_____

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

***Adverse event (s):**

☐Severe local reaction ☐>3 days ☐ beyond nearest joint

☐Seizures ☐ febrile ☐ afebrile

☐ AbscessAbdominal Distention

☐Sepsis ☐Abdominal mass

☐ EncephalopathyPassage of blood per rectum

☐Toxic shock syndromeVomiting of bile-stained fluid

☐ Thrombocytopenia Rectal prolapse or intestinal prolapse

☐ Anaphylaxis

☐ Persistent Fever≥38°C

☐ Other (specify).....

Date & Time AEFI started (DD/MM/YYYY):

__ __ / __ __ / __ __ __ __ ☐☐ Hr ☐☐Min

Describe AEFI (Signs and symptoms) including measure taken:

***Serious: Yes / No ;** ➔If Yes ☐Death ☐Life threatening ☐Disability☐ Hospitalization ☐Congenital anomaly

***Outcome:** ☐ Recovering ☐ Recovered ☐ Recovered with sequelae ☐ Not Recovered ☐ Unknown

☐ Died If died, date of death (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Autopsy done: ☐Yes ☐No ☐Unknown

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

Woreda level to complete:

Date report received at Woredal level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
Investigation needed:☐ Yes☐ No If yes, date investigation planned (DD/MM/YYYY): __ __ / __ __ / __ __ __ __ Comments:

Regional Level to Complete

Date report received at Regional level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
Comments:

National Level to Complete

Date report received at National level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __
Comments:

**Compulsory field*

Annex 2 AEFI LINELIST

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 case(write vertical)	Kebele(write name vertical)	Woreda (write name vertical)	Zone(write name vertical)	Region	Date of birth(dd/mm/yyyy) and	Date of immunisation(dd/mm/yyy y) (write vertical)	Reaction type (code) [1] Minor [2]Severe/Serious (write code only)	Outcome(1)(Recovered disability(2)/Died(3) (write code only)	Suspected vaccine(name and dose, e.g. Penta-2) at t	Vaccine batch/Lot number	Diluent batch number	Onset time interval (hours, days, weeks)	Date reporting (dd/mm/yyyy)

(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:** _____

Annex 3 AEFI CASEINVESTIGATION FORM, ETHIOPIA

AEFI CASE INVESTIGATION FORM

Section A **Basic details**

Region **Zone** **Woreda** **Case ID**

Place of vaccination *()*: Govt. health facility/Private health facility/Other (specify) _____

Vaccination in *()*: Campaign/Routine/Other (specify) _____

Name and Address of vaccination site:

Type of site *()*Fixed Mobile Outreach Other _____

Name of Reporting Officer:

Date of investigation: __ __ / __ __ / __ __ __ __

Date of filling this form:__ __ / __ __ / __ __ __ _

Designation/ Position:

Telephone #: 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*

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

Name of vaccines/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

Date of first/key symptom *(DD/MM/YYYY)*:__ __ / __ __ / __ __ __ __Time of first symptom (*hh/mm):* __ __ / __ __

Date of hospitalization*(DD/MM/YYYY)*: __ __ / __ __ / __ __ __ __

Date first reportedto the health authority *(DD/MM/YYYY)*:__ __ / __ __ / __ __ __ __

Statuson 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 previous vaccination(s)	Yes / No/ Unkn	
History of allergy to vaccine, drug or food	Yes / No/ Unkn	
Pre-existing illness (30 days) / congenital disorder	Yes / No/ Unkn	
History of hospitalization in last 30 days, with cause	Yes / No/ Unkn	
Patient currentlyon 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:

Deliveryprocedure was: Normal___Caesarean___ Assisted (forceps, vacuum etc.)____

Withcomplication (specify)_____

Place of birth: Home__ Health facility_____

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 (e.g. parents)*_____

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) and then complete additional information NOT AVAILABLE in existing documents, i.e.**

- ***If patient has receivedmedical care***attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only theinformation 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 Clinical 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**									

**Write name of vaccine(s) given on the same vaccination day at the site ** Write total doses administered for each vaccine*

- When was the patient immunized? (Tick the box thebelowand 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 givenwithin the first few doses of the vial administered?

Within the last doses of the vial administered?

unknown?

• Was there an error in prescribing or non-adherence to recommendations for use of this vaccine?	Yes/ No
• Based on your investigation, do you feel that the vaccine (ingredients) administered could have been unsterile?	Yes/ No/ Unable to assess
• 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
• 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
• 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
• 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
• Number immunized from the concerned vaccine vial/ampoule	
• Number immunized with the concerned vaccine in the same session	
• Number immunized with the concerned vaccine having the same batch number in other locations. Specify locations:_____	
• Is this case a part of a cluster?	Yes / No/ Unkn
• If yes, how many other cases have been detected in the cluster?	
• Did all the cases in the cluster receive vaccine from the same vial?	Yes / No/ Unkn
• If no, number of vials used in the cluster (enter details 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 (√)	Yes	No	NA
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:

Section F Cold chain and transport *(Complete this section by asking and/or observing practice)*			
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes	No	Unkn
oIf "yes", was there any deviation outside of 2−8◦ C after the vaccine was placed inside?			
oIf "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
Last vaccine storage point:			
• Is the temperature of the vaccine storage refrigerator monitored?	Yes/No		
oIf "yes", was there any deviation outside of 2−8◦ C after the vaccine was placed inside?	Yes / No		
oIf "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	Yes	No	Unkn
• 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:			
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
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	Unkn

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 4 AEFI LABORATORY REQUEST FORM

AEFI – LABORATORY REQUEST FORM (LRF)
(should be accompanied with specimens)

(For Serious Adverse Events Following Immunization)

AEFI category (Encircle): **Death / Hospitalized / Cluster / Disability**

Region		**Case ID**	
Zone			
Woreda			

Name of person sending the specimen:	Date of filling LRF :
Designation:	
Phone Number :	

Case Name	

Date of Birth	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*		Age (in months)				Sex	Male	Female										

Complete Address of the patient with landmarks *(kebele, house number, village, block, Telephone No. etc.)*

P	**H**	**O**	**N**	**E**	**-**																					

Date of vaccination	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*	Date of Onset	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*									
Date of collection of specimen	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*	Time of collection of specimen	*H*	*H*	*M*	*M*	*(*	*AM*	*PM*	*)*									

. Precise description of samples:
a) For vaccine/diluents specimens: (to be transported in reverse cold chain)

Annex 5. **Worksheet for causality assessment**

Step 1: **Eligibility**

Name of the patient	Name of one or more vaccines administered before this even	What is the valid diagnosis?	Does the diagnosis meet a case definition?

Create your question on causality here

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

Step 2: **Event checklist**

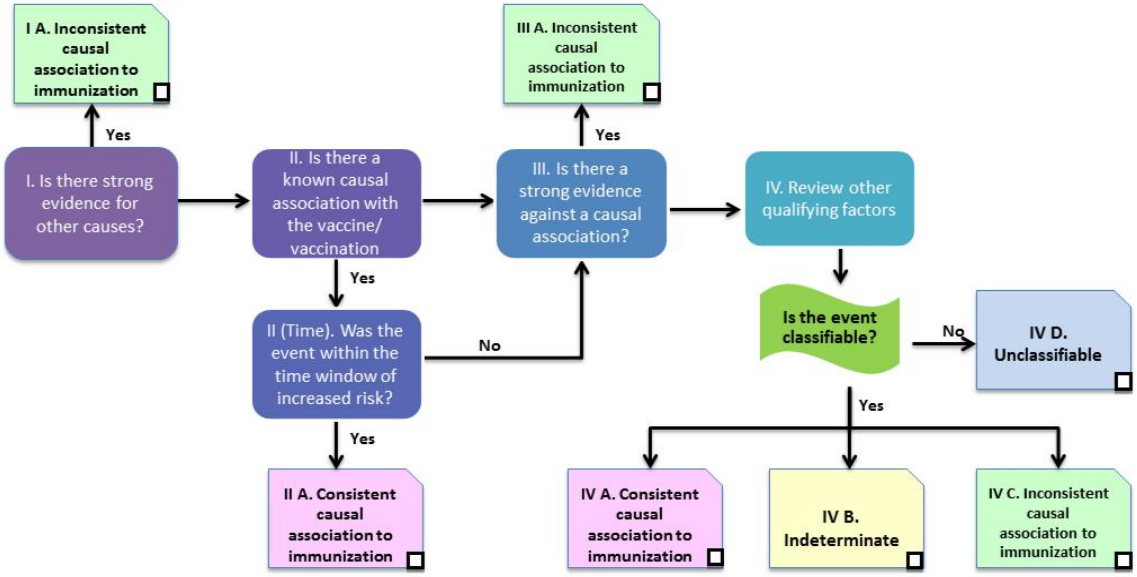
Check all boxes that apply

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

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

Step 3: **Algorithm**

Review all steps and check all the appropriate boxes



Notes for step 3:

Step 4: **Classification**

Check all boxes that apply

Adequate information available

A. Consistent causal association to immunization

- ☐ A1. Vaccine product-related reaction (As per published literature)
- ☐ A2. Vaccine quality defect-related reaction
- ☐ A3. Immunization error-related reaction
- ☐ A4. Immunization anxiety-related reaction

B. Indeterminate

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

C. Inconsistent causal association to immunization

- ☐ C. Coincidental Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine

Adequate information not available

☐ Unclassifiable

Specify the additional information required for classification :

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

Summarize the classification logic:

With available evidence, we could conclude that the classification is _____because

ANNEX 6: RECOGNITION AND TREATMENT OF ANAPHYLAXIS

Anaphylaxis is a very rare (estimated as once every million doses of vaccine given) but severe and potentially fatal allergic reaction. When anaphylaxis does occur, the patient must be diagnosed properly, treated and managed urgently by trained staff and transferred to a hospital setting. There is a high risk that health workers who lack training will misdiagnose faints (vasovagal syncope) and dizziness following immunization for the onset on anaphylaxis. Most episodes of feeling ill or faint, or actual fainting that occur immediately after immunization are not due to the onset of anaphylaxis. The administration of adrenaline in faints is not only contraindicated, it is very dangerous. Therefore, health workers should be trained on distinguishing fainting, anxiety and breath-holding from anaphylaxis following vaccine administration.

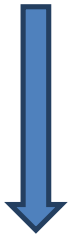
a. **Fainting**: Very common in adolescents and adults, the individual suddenly becomes pale, loses consciousness and collapses to the ground (unless supported). Fainting is sometimes accompanied by brief clonic seizure activity (i.e., rhythmic jerking of the limbs), but this requires no specific treatment or investigation. It is managed by simply placing the patient in a recumbent position. Recovery of consciousness occurs within a minute or two, but patients may take some more time to recover fully.

b. **An anxiety spell** can lead to a pale, fearful appearance and symptoms of hyperventilation (light-headed, dizziness, tingling in the hands and around the mouth).

c. **Breath holding** occurs in young children and will lead to facial flushing and cyanosis. It can end in unconsciousness, during which breathing resumes.

d. **Anaphylaxis** is a severe reaction of rapid onset (usually 5-30 minutes after the injection) characterized by circulatory collapse. The early signs of anaphylaxis are generalized erythema and urticaria with upper and/or lower respiratory tract obstruction. In more severe cases, limpness, pallor, loss of consciousness and hypotension become evident. Most life-threatening reactions begin within 10 minutes of vaccine administration. Unconsciousness is rarely the sole manifestation of anaphylaxis - it only occurs as a late event. Presence of strong central pulse rules out anaphylaxis.

Recognition of Anaphylaxis

Clinical Progression	Signs and symptoms of anaphylaxis
Mild, early warning signs 	• Itching of the skin, rash and swelling around injection site. • Dizziness, general feeling of warmth • Painless swellings in part of the body e.g., face or mouth. Flushed, itching skin, nasal congestion, sneezing, tears. • Hoarseness, nausea, vomiting • Swelling in the throat, difficulty breathing, abdominal pain
Late, life-threatening symptoms	- Wheezing, noisy, difficulty breathing, - Collapse, low blood pressure, irregular weak pulse

Treatment of anaphylaxis

- ***Principle***: Once the diagnosis is made, consider the patient as being in a potentially fatal condition, regardless of the severity of the current symptoms. Begin treatment immediately and, at the same time, make plans to transfer the patient swiftly to hospital (if not already in a hospital setting).
- ***Steps in initial management***

1. If already unconscious, place the patient in the recovery position and ensure the airway is clear.
2. Assess heart rate and respiratory rate (if the patient has a strong carotid pulse, he/she is probably not suffering from anaphylaxis).
3. If appropriate, begin cardiopulmonary resuscitation.
4. Give 1:1000 adrenalines (see below for correct dose for age or weight) by deep intramuscular injection into the opposite limb to that in which the vaccine was given. (Subcutaneous administration is acceptable in mild cases).
5. Give an additional half dose around the injection site (to delay antigen absorption).
6. If the patient is conscious after the adrenaline is given, place his/her head lower than the feet and keep the patient warm.
7. Give oxygen by face mask, if available.
8. Call for professional assistance but never leave the patient alone. Call an ambulance (or arrange other means of transport) after the first injection of adrenaline, or sooner if there are sufficient people available to help you.
9. If there is no improvement in the patient's condition within 10-20 minutes, of the first injection, repeat the dose of adrenaline up to a maximum of three doses in total. Recovery from anaphylactic shock is usually rapid after adrenaline.
10. Record, or get someone to record, vital signs (pulse rate, respiratory rate and blood pressure), as well as time and exact dose of any medication given. Make sure the details accompany the patient when he is transferred. Mark the immunization card clearly so the individual never gets a repeat dose of the offending vaccine. At a suitable moment, explain to parents or relatives the importance of avoiding the vaccine in the future.
11. Report the occurrence of anaphylaxis to the appropriate woreda officer in the Ministry of Health and EFMHACAby e-mail, fax or phone when the clinical situation is dealt with.

Adrenaline dosage

- **General Dose**: Give 1:1000 adrenalines (epinephrine) at a dose of 0.01ml/kg up to a maximum of 0.5 ml injected intramuscularly (or subcutaneously in very mild cases)
- If the weight of the patient is unknown, refer to the following table.

Age	Dose
Less than 2 years	0.0625 ml(1/16th of a ml)
2-5 years	0.125 ml (1/8th of a ml)
6-11 years	0.25 ml (1/4 of a ml)
11+ years	0.5 ml (1/2 of a ml)

Prevention of death in anaphylaxis

- Train health workers on recognition and treatment of anaphylaxis
- Injectable vaccines should always be given in fixed posts having access for immediate transport services to health center and/or hospital.
- Vaccinators should be equipped with minimum packages of AEFI kits (e.g. adrenaline with syringes).
- Always keep the recipient under observation for at least 20 minutes after the injection.
- Campaigns should always be supervised by experienced health workers with clinical skills.

Annex 7. Frequency of Vaccine Adverse Reactions of commonly used vaccines

BCG Vaccine Summary

Vaccine Adverse Reactions	Frequency category
Injection site reaction (Papule, mild ulceration orscar)	Very common
Suppurative lymphadenitis	Uncommon to Rare
BCG osteitis	Uncommon to Very rare
Disseminated BCG disease or systemic BCG-itis	Very Rare
Immunine Reconstitution Inflammatory Syndrome (IRIS)	Very Rare

DTP Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Whole cell Pertussis vaccines	
Fever 100.1₀F - 102₀F	Very common
Injection site Redness	Very common
Swelling	Very common
Pain (Severe-Moderate)	Very common
Fussiness (Severe-Moderate)	Very common
Drowsiness	Very common
Anorexia	Very common
Vomiting	Common
Persistent screaming	Uncommon to Rare
HHE	Very rare
Seizures	Very rare
Encephalopathy	Very rare
Anaphylaxis	
Acellullar Pertussis vaccines	
Fever 100.1₀F - 101₀F	Very common
Fever 100.1₀F - 102₀F	Common
Injection site Redness	Common to Very common
Injectionsite swelling	Common to Very common
Pain (Severe-Moderate)	Uncommon to Common
Fussiness (Severe-Moderate)	Common to Very common
Drowsiness	Very Common Very
Anorexia	Common
Vomiting	Very Common
Persistent screaming	Uncommon
HHE	Rare
Seizures	Very rare

Hepatitis B Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common
Headache	Common
Injection site pain	Common to Very common
Injection site redness	Common
Injection site swelling	Common
Anaphylaxis	Very rare

Human Papiloma Vaccines (HPV) Summary

Vaccine Adverse Reactions	Frequency category
Bivalent HPV Vaccine	
Fever	Common
Headache	Very common
Injection site pain	Very common
Redness	Very common
Swelling	Very common
Rash	Uncommon
Arthralgia	Very common
Myalgia	Very common
Fatigue	Very common
Gastrointestinal disorders	Very common
Quadrivalent HPV Vaccine	
Fever 100.1₀F - 101₀F	Very common
Fever 100.1₀F - 102₀F	Very Common
Injection site Redness	Common
Injectionsite swelling	Common
Pain (Severe-Moderate)	Common
Fussiness (Severe-Moderate)	Common
Drowsiness	Common
Anorexia	Common
Vomiting	Common
Persistent screaming	Common
HHE	Very common
Seizures	Very rare

Tetanus vaccines Summary

Vaccine Adverse Reactions	Frequency category
Brachial neuritis	Very rare
Anaphylaxis	Very rare

Hib Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common
Injection site reaction	Very common

Polio Vaccines Summary

Vaccine Adverse Reactions	Frequency category
VAPP	
– Recipient VAPP	Very Rare
– Total VAPP	Very Rare
Inactivated Polio Vaccine (IPV)	
Injection site erythema	Un common to Common
Injection site induration	Common to Very common
Injection site tenderness	Very Common

Measles Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common to Very common
Rash	Common
Injection site reaction	Very common
Febrile seizures	Rare
Encephalomyelitis	Very rare
Thrombocytopenia	Very rare
Anaphylaxis	Very rare

Pneumococcal vaccines Summary

Vaccine Adverse Reactions	Frequency category
Unconjugated vaccine (PPSV)	
Fever > 39$_{o}$C	Uncommon
Injection site reaction	Very common
Conjugated vaccine (PCV)	
Fever > 39$_{o}$C	Uncommon
Injection site reaction	Very common

Rubella Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Fever	Common
Injection site reaction	Very common
Acute Arthralgia (adults)	Very common
Acute Arthritis (adults)	Very common

Rotavirus Vaccines Summary

Vaccine Adverse Reactions	Frequency category
Intussusception	Very rare

Yellow Fever vaccines Summary

Vaccine Adverse Reactions	Frequency category
Vaccine-associated viscerotropic diseases	Very rare

Key

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

Source: WHO Fact sheets
www/who.int/vaccinessafety/initiative/tools/vaccinfosheets

Annex 8: **AEFI Monitoring Indicators**

GACVS considered a number of principles in deriving a set of indicators for AEFI surveillance. Three types of indicators are proposed: (i) to monitor the volume of AEFI reports; (ii) to monitor the quality of those reports; and (iii) to monitor the quality of the response to serious AEFI.

1. **AEFI Reporting Rate**: It is the primary indicator and estimated as number of all AEFI casesreported per 100,000 live births per year.

$$\text{AEFI Reporting Rate} = \frac{No.\,of\ all\ reported\ AEFIs\ in\ a\ year}{Total\ Live\ births\ during\ the\ same\ year} x\ 100{,}000$$

   The minimum target for this indicator is 10 AEFI cases per 100,000 live births

2. **Proportion of AEFI Cases Investigated**: This measures the quality of AEFI surveillance system and measured as proportion of reported cases for which AEFI Case Investigation form (annex 3) is filled. There is no standard target. However, all AEFI cases warranting detail field investigation should have the form filled and documented at national level.

3. **AEFI case fatality Rate**: This measures the quality of care for responding to serious AEFI cases reported. It is the percentage (%) of deaths occurred per AEFI cases reported.
4.
5. **Proportion of serious AEFI cases classified by causality assessment committee**: it measures the presence and functionality of an independent vaccine safety monitoring body that reviews and classifies all serious cases. It is calculated as no. of cases reviewed and classified per serious cases reported to the national level.
   Target: All serious cases should be reviewed and classified within one month of report.
6.
7. **Frequency of Vaccine Safety Monitoring Meetings**: A quarterly meeting (e.g. AEFI taskforce, casualty assessment committee, etc.) is expected to be held for monitoring AEFI and other vaccine safety issues.

8. **Other supplementary indicators (Proposed)**
   - Timeliness of reporting of suspected AEFIs
   - Timeliness of investigation of notified AEFIs
   - Availability of AEFI database at national level
   - Availability of designated AEFI focal person at health facility level
   - Availability of trained AEFI focal person at woreda level

Annex 9: Standard Operating Procedures for AEFI Detection