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THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES FOR SURVEILLANCE OF ADVERSE EVENTS FOLLOWING IMMUNIZATION

(Made under Regulation 4 (1) of the Tanzania Medicines and Medical Devices (Pharmacovigilance) Regulations, 2018)

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Foreword

Tanzania Medicines and Medical Devices Authority (TMDA) was established under the Tanzania Medicines and Medical Devices Act, Cap 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of medicines, medical devices, diagnostics and other health related products. To achieve this mission, TMDA collaborates with Immunization and Vaccine Development (IVD) program and other stakeholders in monitoring the safety of vaccines used in Tanzania for immunization.

In Tanzania, AEFI surveillance system and Vaccine Safety in general are well coordinated to improve public health through detection of AEFI and communicating the findings in a timely manner. An effective and well-functioning AEFI surveillance system will contribute to assessing risks, benefits and effectiveness of vaccines which will in turn minimize harm and risks while maximizing known benefits, hence in due course, boost public trust and confidence, as well as improve the quality of the immunization Programme in the long run.

It is therefore essential that all stakeholders like IVD, TMDA, Vaccine Manufacturers, Laboratories and Healthcare Providers make concerted efforts to continue providing documented evidence through an effective AEFI surveillance system. This will ensure that the best immunization services are provided to the community including effective monitoring and response to AEFIs.

The goals of these guidelines are to improve the effectiveness and quality of AEFI surveillance activities consequently strengthening the quality of immunization programme at all levels and to ensure the immunization safety of all recipients of vaccines.

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GLOSSARY OF TERMS

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 unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse Event of Special Interest (AESI): A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.

Anaphylaxis: An acute, potentially lethal, multisystem syndrome resulting from sudden release of mast cell- and basophil derived mediators into the circulation. It is triggered by the binding of allergen to specific immunoglobulin E (IgE).

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.

HIV: Human Immunodeficiency Virus

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 safety Surveillance: A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.

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 stress related responses (ISRR): Stress response to immunization that may manifest just prior to, during, or after immunization.

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 ex- posed 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).

Mass vaccination campaign: Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.

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 verification action.

Surveillance: The continuing, systematic collection of data those are analysed and disseminated to enable decision-making and action to protect the health of populations.

Syncope: Is a temporary loss of consciousness caused by a decreased blood flow to the brain. Although fainting has a variety of possible causes, it is usually triggered by pain or anxiety.

Trigger event: A medical incident following immunization that stimulates a response, usually a case investigation.

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.

Vaccination failure: Vaccination failure can be defined based on 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).

Vaccine pharmacovigilance: The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine(s) or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

Vaccine product-related re- action: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).

Vaccine quality defect related reaction: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.

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 that 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.

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-associated enhanced diseases (VAED): Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.

VigiBase: WHO global database of individual case safety reports (ICSRs) including ADRs and AEFIs, maintained by Uppsala Monitoring Centre.

ABBREVIATIONS

ADRs	-	Adverse Drug Reactions
AEFI	-	Adverse Events Following Immunization
BCG	-	Bacillus Calmette-Guerin
CHMTs	-	Council Health Management Teams
CIOMS	-	Council of International Organizations of Medical Sciences
COVID-19		Corona Virus Disease 2019
DIVO	-	District Immunization and Vaccination Officer
DMO	-	District Medical Officer
DPharm		District Pharmacists
DTP-HepB-Hib	-	Diphtheria Tetanus Acellular Pertussis, Hepatitis B and Haemophilus influenza type b
DTwP	-	Diphtheria Tetanus Whole Cell Pertussis
EPI	-	Expanded Programme on Immunization
FEFO	-	First Expired First Out
FIFO	-	First In First Out
GIVS	-	Global Immunization Vision and Strategy
IPV	-	Inactivated Polio Vaccine
ISRR	-	Immunization stress-related response
IVD	-	Immunization and Vaccine Development Programme
MDVP	-	Multi-Dose Vial Policy
MMR	-	Measles Mumps Rubella
MNH	-	Muhimbili National Hospital
MoH	-	Ministry of Health
NHLQAC	-	National Health Laboratory Quality Assurance Training Centre
NRA	-	National Regulatory Authority
OPV	-	Oral Polio Vaccine
PSURs	-	Periodic Safety Update Reports
RHMTs	-	Regional Health Management Teams
RIVO	-	Regional Immunization and Vaccination Officer
R-Pharm	-	Regional Pharmacist
SARS-Cov-2	-	Severe acute respiratory syndrome coronavirus 2
TITAG	-	Tanzania Immunization Technical Advisory Group
TMDA	-	Tanzania Medicines and Medical Devices Authority
TTCIH	-	Tanzania Training Center for International Health
UDOM	-	University of Dodoma
VAPP	-	Vaccine Associated Paralytic Poliomyelitis
VPD	-	Vaccine Preventable Disease
VVM	-	Vaccine Vial Monitor
WHO	-	World Health Organization
ZFDA	-	Zanzibar Food and Drugs Agency

1. INTRODUCTION

Vaccines are biological substances that are administered to individuals to elicit immunity (protection) against specific diseases. Such products may be formulated together with adjuvants and/or excipients, and like all medicinal products, vaccines may cause adverse events following their administration to some individuals. Despite the fact that serious, vaccine related reactions are rare, and common reactions are minor and self-limited, measures still need to be put in place to monitor and prevent the occurrence of adverse event following immunization (AEFI), and when needed to take appropriate regulatory action(s) on the products themselves.

AEFI arises from different causes including: inherent vaccine product related, quality defect related, immunization error related, immunization anxiety related, coincidental or events undetected during pre-licensure clinical trials. A robust AEFI surveillance system in a country will help authorities detect, manage and prevent AEFIs and hence protect and promote public health.

In Tanzania, the Ministry of Health (MoH) operates the Immunization and Vaccine Development (IVD) Programme. IVD is responsible for setting up policy guidelines and standards for selection, supply and utilization of vaccines in the country. IVD has done and continues to do a tremendous job. Some of the notable achievements of the programme include achieving immunization coverage of over 90% for all primary immunization; establishing a cold chain system; introducing new vaccines such as Human Papillomavirus Vaccine (HPV), COVID-19 vaccines and novel Oral Poliovaccine-2 (nOPV2), engaging regional and district authorities in monitoring vaccine use, training and developing healthcare providers as well as establishing linkages and networking with international stakeholders.

Likewise, TMDA monitors the safety of medical products including vaccines. TMDA primarily uses spontaneous pharmacovigilance system to collect AEFI experienced by vaccine recipients. TMDA is also responsible for authorization of marketing for all medicines including vaccines. All vaccine manufacturers are required by law to register their products before supplying and distributing them in the country and to establish safety monitoring for the products they place in the market.

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

These comprehensive and updated guidelines outline processes and procedures to be followed by healthcare providers in reporting, documenting, investigating and preventing AEFIs, as well as the roles and responsibilities of different stakeholders responsible for the planning and delivery of immunization programs in Tanzania in close partnership. The guidelines also outline the surveillance system and provide tools and procedures needed to report AEFIs. An understanding of the types of AEFIs, investigation techniques, specimen collection managing AEFIs and communication including communicating with the media, are also delineated in this document.

This second version of the guidelines for surveillance of AEFI in Tanzania incorporates current and available information on the topic. Particularly, it draws lessons gained from COVID-19 vaccines. The guidelines also include revised tools for surveillance of AEFI such as AEFI reporting form and AEFI investigation form. It also includes quick guide to be followed during investigation of AEFI as well as a format for linelisting of AEFI. It is anticipated that healthcare providers at the national, regional and district levels; staff of pharmacovigilance centers; immunization service providers and other stakeholders in immunization service in the country will read and make a good use of these guidelines and thus improve the efficiency and quality of AEFI surveillance system in the country. Consequently, strengthening the quality of immunization programmes at the regional and national levels – and ensure that the safety of vaccines recipients in the country is protected and subsequently protect the public from the vaccine preventable diseases (VPD).

2.0 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.

2.2 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. bOPV contains two attenuated polio virus serotypes 1 and 2 and IPV contains killed poliovirus serotypes 1, 2, and 3).

Combination (or combined) vaccines contain two or more different antigens (e.g. DTwP, DTP-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 programme.

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.

2.3 Other components of vaccines

In addition to the primary antigen(s), vaccines may contain small quantities of other substances such as adjuvants, antibiotics, preservatives and stabilizers. Sometimes AEFI may result from one of these other substances.

Adjuvants: Substances added to a vaccine to enhance the immune response, thus making it possible, in some cases, to reduce the amount of antigen (immunogen) per dose or the total number of doses needed to achieve immunity.

Antibiotics: These are used during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown.

Preservatives: These are chemicals (e.g. thiomersal, phenol derivatives) that are added to killed or subunit vaccines in order to inactivate viruses, detoxify bacterial toxins, and 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: Stabilizers are used to help the vaccine maintain its effectiveness during storage.

2.4 Classification of vaccines

There are six (6) types of vaccines:

a) Live-attenuated vaccines (LAV)

b) Inactivated vaccine (killed antigen)

c) Nucleic acid vaccines (RNA, DNA)

d) Subunit vaccines (purified antigen)

e) Toxoid vaccines (inactivated toxins)

f) Viral vector vaccines

Characteristics of these vaccines differ, and the characteristics determine how the vaccine works **(Table 1).**

a) Live-attenuated vaccines

Live Attenuated Vaccines (LAV) are derived from “wild,” or disease-causing, virus or bacteria. Wild viruses or bacteria are attenuated, or weakened, in a laboratory, by repeated culturing. The resulting vaccine organism retains the ability to replicate (grow) in the vaccinated person and produce immunity, but usually causes no illness, or disease. The immune response to a LAV is virtually identical to that produced by a natural infection. For LAV, the one dose usually provides protection. The second dose given as an additional opportunity to achieve immunity in more than 95% of individuals. Immunity following live vaccines is long-lasting, and booster doses are usually not necessary, except for oral polio vaccine, which requires multiple doses. Generally, LAV are labile thus can be damaged or destroyed by heat and light, therefore, LAV need to be handled and stored appropriately. Examples of live attenuated vaccines include oral poliovirus vaccine, measles vaccine, mumps vaccine, rotavirus vaccine, rubella vaccine, yellow fever and BCG vaccine.

b) Inactivated (killed) vaccines

Inactivated vaccines, are produced by growing viruses or bacteria in culture media and then inactivating them with heat or chemicals. Formaldehyde is the chemical usually used, but later removed almost entirely during the purification process. Inactivated vaccines are generally safer than live attenuated vaccines because they are not alive, they cannot grow in a vaccinated individual and, therefore, cannot cause the disease, even in someone with immunodeficiency.

Inactivated antigens are not affected by the circulating antibodies and often more stable than live attenuated vaccines. Inactivated vaccines usually require multiple doses, one dose is not enough to produce protective immunity, but only “primes” the immune system. A protective immune response develops after multiple subsequent doses.

In contrast to live attenuated vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral, and results in little or no cellular immunity. Antibody titers against inactivated antigens diminish over time, thus, some inactivated vaccines may require periodic supplemental doses to increase, or “boost,” antibody titers to reach protective threshold.

Examples of whole-cell inactivated vaccines include; Virus - Inactivated Polio Vaccine (IPV); COVID-19 vaccines manufactured by Sinopharm and Sinovac by growing the virus in Vero cells and bacteria – whole cell Pertussis (wP).

c) Nucleic acid vaccines

Nucleic acid vaccines use genetic material from a disease-causing virus or bacterium (a pathogen) to stimulate an immune response against it. Depending on the vaccine, the genetic material could be DNA or RNA; in both cases it provides the instructions for making a specific protein from the pathogen, which the immune system will recognize as foreign (an antigen). Once inserted into host cells, this genetic material is read by the cell’s own protein-making machinery and used to manufacture antigens, which then trigger an immune response.

Nucleic acid vaccines are further categorized into two groups:

i) Messenger RNA (mRNA) vaccines
ii) DNA vaccines

Examples of nucleic vaccines include Pfizer-BioNTech (BNT162b2) COVID-19 vaccine and Moderna (mRNA-1273) COVID-19 vaccine.

d) Subunit (Purified antigen) Vaccines

Subunit vaccines, like inactivated whole-cell vaccines, do not contain live components of the pathogen. They differ from inactivated whole-cell vaccines, by containing only the antigenic parts of the pathogen. These parts are necessary to elicit a protective immune response. Antigenic properties of the various potential subunits of a pathogen must be examined in detail to determine which particular combinations will produce an effective immune response within the correct pathway. Often a response is elicited, but there is no guarantee that immunological memory will be formed in the correct manner. Thus, they need booster. Like inactivated vaccines, subunit vaccines do not contain live components and are considered as very safe.

Subunit vaccines are categorized into three groups:
i) Protein based
ii) Polysaccharide based
iii) Conjugate vaccines

2.4.1.1 Protein-based subunit

a) Protein based subunit vaccines present an antigen to the immune system using a specific, isolated protein of the pathogen. A weakness of this technique is that isolated proteins, if denatured, may bind to different antibodies than the protein of the pathogen.

Commonly used protein-based subunit vaccines are the following: - **Acellular pertussis (aP)**
vaccines contain inactivated pertussis toxin (protein) and may contain one or more other bacterial components. The pertussis toxin is detoxified either by treatment with a chemical or by using molecular genetic techniques then attached.

b) Hepatitis B
vaccines are composed of the hepatitis B virus surface antigen (HBsAg), a protein produced by hepatitis B virus. The hepatitis B vaccine produced 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 harvested, purified 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.

c) Novavax (NVX-CoV2373)
vaccines consist of a recombinant SARS-CoV-2 spike protein nanoparticle delivered using saponin-based Matrix-M adjuvant.

2.4.2 Polysaccharide subunit vaccines

Polysaccharide-based vaccines are composed of long chains of sugar molecules taken from the surface capsule of the bacteria. Some bacteria, when infecting humans protected by a polysaccharide (sugar) capsule that helps the organism evade the human defense systems, especially in infants and young children. Polysaccharide vaccines provoke an immune response against this capsule; however, they are not very immunogenic and induce only short-term immunity (slow immune response, slow rise of antibody levels, poor immune memory). Because of their low immunogenicity, they are not effective in infants and young children (under 18–24 months).

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

2.4.3 Conjugated subunit vaccines

Pure polysaccharide vaccines are generally not effective in children under the age of two years unless coupled with a protein. This coupling process called “conjugation.” When these polysaccharide antigens linked chemically (Conjugated) to a protein that T-cells recognize, and then these conjugate vaccines can elicit strong lasting immune responses and immune memory in young children. In comparison to pure polysaccharide subunit vaccines, conjugated vaccines induce a long-term protective immune response even in infants therefore prevent common bacterial infections for which plain polysaccharide vaccines are either ineffective in those most at risk (infants) or provide only short-term protection (everyone else). The advent of conjugate subunit vaccines heralded a new age for immunization against diseases caused by encapsulated organisms such as meningococcus and Haemophilus influenza type b (Hib). Examples of conjugated vaccines include Haemophilus influenzae type b (Hib), pneumococcal (PCV-7, PCV-10, PCV-13) and meningococcal A.

e) Toxoid Vaccines (Inactivated toxic compound)

A vaccine made from a toxin (poison) that been made harmless but elicits an immune response against the toxin. Toxoid vaccines based on the toxin produced by certain bacteria (e.g. tetanus or diphtheria). The protein-based toxin is rendered harmless (Toxoid,

Inactivated or killed toxin (poison) used in vaccine production) and used as the antigen in the vaccine to elicit immunity.

Table 1: Classification of vaccines

Type	Examples
Live attenuated vaccines (LAV)	Bacteria: BCG vaccine
	Virus: Live Japanese encephalitis vaccine, 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 Japanese encephalitis vaccine, Inactivated Poliovirus Vaccine (IPV), Hepatitis A vaccine, Rabies Vaccine BBIBP-CorV (Sinopharm COVID-19 vaccine); CoronaVac (Sinovac COVID-19 vaccine)
Subunit vaccines (purified antigens)	Protein-based: Hepatitis B vaccine Acellular pertussis vaccine(aP) NVX-CoV2373 (Novavax Covid-19 vaccine)
	Polysaccharide: Meningococcal polysaccharide vaccine Pneumococcal polysaccharide vaccine Typhoid Vi polysaccharide vaccine
	Conjugate vaccine: *Haemophilus influenza* 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
Nucleic acid vaccines	RNA vaccines: Pfizer-BioNTech (BNT162b2) vaccine, Moderna (mRNA-1273)
	DNA vaccines: ZyCoV-D
Viral vector-based vaccine	ChAdOx1-S (AZD1222 – COVID-19 vaccine) developed by Oxford/AstraZeneca Ad26.COV 2.S developed by Johnson & Johnson Sputnik V by Gamaleya Research Institute Ebola vaccine (rVSV-ZEBOV)

To increase the immune response, the toxoid is adsorbed to aluminium or calcium salts, which serve as adjuvants 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. While no longer toxic, the toxoid is still capable of inducing a specific immune response protective against the effects of the toxin. To increase immune response, toxoid is adhered to an adjuvant (ex. Aluminium salts). Toxoids are not highly immunogenic and require booster doses. Examples of toxoid vaccines include Tetanus toxoid and Diphtheria toxoid vaccines.

f) Viral vector-based vaccines

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

2.4.4 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 are not contraindications, but are events or conditions that should be considered in determining if the benefits of the vaccine outweigh the risks (especially if the would-be recipient is immunocompromised or pregnant). Precautions stated in the product labelling may sometimes be inappropriately interpreted as contraindications, resulting in missed opportunities to vaccinate. Therefore, HCW need to have a clear understanding of contraindications and precautions. Since precautions are not contraindications, therefore 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. The vaccines that are recommended in pregnancy will benefit and protect both mother and newborn.

Generally, before vaccinating, HCWs should verify the product information on vaccine and diluent vial labels, check for vaccine contraindications, as indicated in the product information leaflet. A clear communications strategy prior to vaccine introduction is also critical to ensure the right safety messages are communicated prior to, during and after mass immunization campaigns in order to maintain public trust in the immunization programme if any serious AEFI occurs.
In addition, appropriate measures to prevent Immunization Stress-Related Response (ISRR) during mass immunization programmes should be taken, e.g., separate areas for waiting, vaccination, and if necessary, for observation after vaccination.

2.4.5 Adverse Events Following Immunization

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

There are five categories of AEFI as defined by the Council of International Organizations of Medical Sciences (CIOMS) and WHO are described in **Figure 1.**

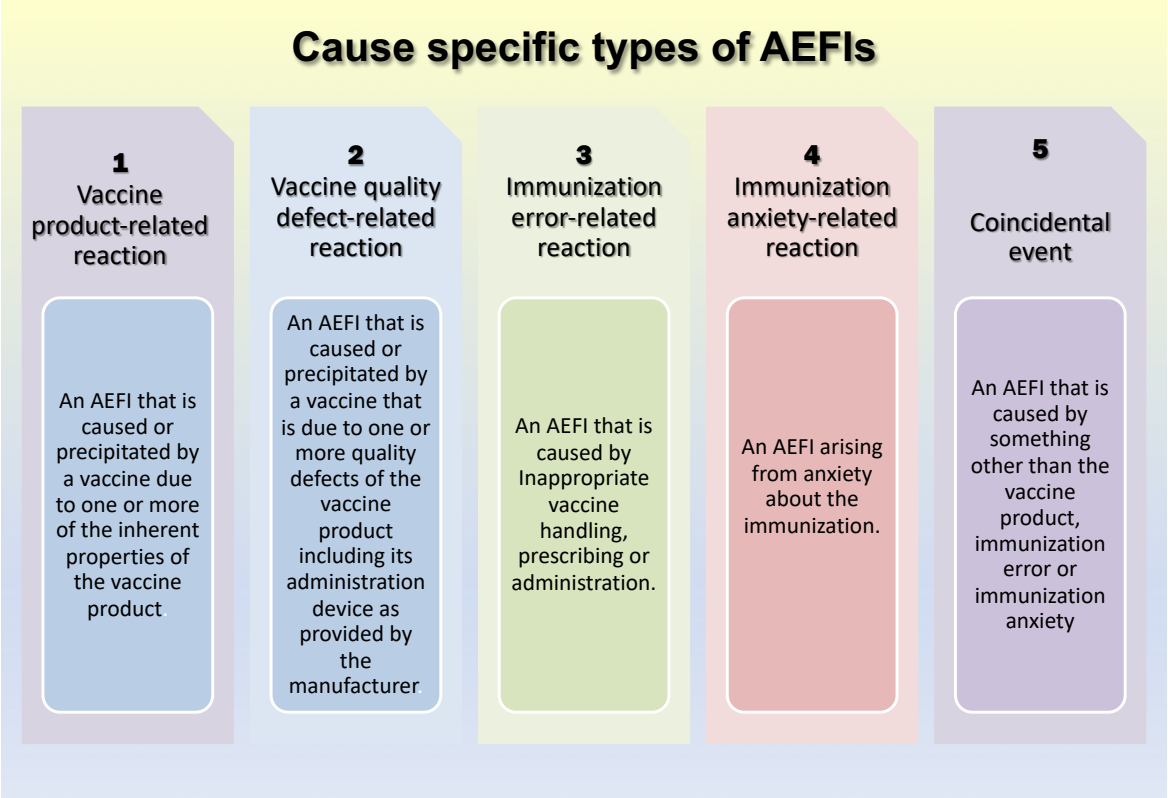


Figure 1: Cause-specific categorization of AEFI (CIOMS/WHO 2012)

Note: "Immunization" as used in these definitions 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.

2.4.6 Vaccine reactions

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

a) Cause-specific vaccine reactions:
i) vaccine product-related reaction and
ii) vaccine quality defect-related reaction
b) Vaccine reactions by seriousness and frequency:
i) common or minor reactions;
ii) rare or serious reactions

2.4.7 Cause-specific vaccine reactions

i. ***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).

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

This is a 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.

2.4.8 Vaccine reactions by seriousness and frequency

Most vaccine reactions are minor and subside on their own. Serious reactions related to vaccines are very rare and, in general, do not result in death or long-term disability. Frequent categories of occurrence of reported adverse events are indicated in **Table 2** below**.**

Table 2: 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%

i. 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 AEFIs are minor and settle on their own. Minor AEFI could be local or systemic.

Local reactions include pain, swelling and redness at the injection site. Systemic reactions include fever irritability and malaise.
For COVID-19 vaccines, the expected common reactions include headache, fatigue, muscle and joint pain, fever and chills and pain at the site of injection. The occurrence of these adverse events is consistent with what is already known about the vaccines from clinical trials.

Generally, a successful vaccine reduces these reactions to a minimum while producing the best possible immunity. **Table 3** describes the common minor vaccine reactions by antigen and recommended treatment for the same.

It is important to note that these vaccine reaction rates are an expected response to the vaccine antigen. In Tanzania, minor reactions are also reportable. Reporting minor reactions is equally important because it helps to understand the observed reactions rates for vaccines. If the observed rate of vaccine reactions is significantly higher than the expected vaccine reaction rate for any vaccine, an investigation is needed to explain this.

Table 3: Common minor vaccine reactions by antigen and treatment

Vaccine	Local adverse events (pain, swelling, redness)	Fever (> 38 °C)	Irritability, malaise and systemic symptoms
BCG1	**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/Td	**~ 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 antigens in the vaccine.

[2] Diarrhea, 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

ii. 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), persistent inconsolable screaming) etc., do not lead to long-term problems. Anaphylaxis, while potentially fatal, is treatable.

Severe AEFI are considered serious by definition if they:

a) Result in death,
b) Are life-threatening,
c) Requires in-patient hospitalization or prolongation of existing hospitalization,
d) Result in persistent or significant disability/incapacity,
e) Are congenital anomaly/ birth defect.

In addition, any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.

All serious AEFI should be reported, investigated and their causality systematically assessed. The rate of occurrence of the rare and more serious reactions has been summarized in **Table 4**.

Table 4: 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 million[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
	Anaphylaxis	0-1 hour	20
	Encephalopathy	0-2 days	0-1

Notes:

1. Seizures are mostly febrile and the risk depends on age, with much lower risk in infants under the age of 4 months. 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).
2. Reactions (except anaphylaxis) do not occur if already immune (~90% of those receiving a second dose are immune).
3. 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 immunocompromised.

2.4.9 Prevention and Management of Vaccine Reactions

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. 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.

Every health facility should have an emergency kit consisting of adrenaline (1:1000), hydrocortisone, analgesics, anti-inflammatory agents, normal saline and injection equipment (2 mls and 10 mls syringes), needles and intravenous giving sets.

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 vaccinee. A febrile child can be cooled with a tepid sponging or bath, and by wearing light cool clothing. Extra fluids need to be given to children with fever. For a local reaction, a cold cloth applied to the site may ease the pain. Using local remedies for any serious vaccine reaction can risk the health and life of the vaccinee 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.

An advice should be given to caretakers on managing of common minor reactions, and in addition to instruction on seeking proper medical care if there are severe symptoms. Such action will help to reassure parents about immunization and prepare them for common reactions.

2.4.10 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 preventable and identification and correction of these errors in a timely manner are important (**Table 5**).

Table 5: Examples of Immunization error-related reactions

Immunization error	Possible AEFI
Non-sterile injection Re-use of disposable syringe or needle leading to contamination of the vial, especially in multi-dose vials, Improperly sterilized syringe or needle Contaminated vaccine or diluent.	Local injection site reactions (e.g., abscess, swelling, cellulitis, induration), Sepsis, Toxic shock syndrome, Blood-borne transmission of disease, e.g., hepatitis B, HIV, Death.
Reconstitution error Inadequate shaking of vaccine, Reconstitution with incorrect diluent, Drug substituted for a vaccine or diluent, Re-use reconstituted vaccine at subsequent session	Local abscess, Vaccine ineffective*, Effect of drug, eg., insulin, oxytocin, muscle relaxants, Toxic shock syndrome, Death.
Injection at incorrect site	Local reaction or abscess or other local

Immunization error	Possible AEFI
• BCG given subcutaneously, • DTP/DT/TT given too superficial • Injection into buttocks	reaction, • Sciatic nerve damage
Vaccine transported/stored incorrectly	• Increased local reaction from frozen vaccine, • Ineffective vaccine
Contraindication ignored	Avoidable severe reaction

*Ineffective vaccine is not strictly an adverse event it is a vaccine failure

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 a single or multiple vial of vaccine that have been contaminated or inappropriately prepared. For instance, freezing vaccine during transport may lead to an increase in local reactions. Cluster of reactions requires a systematic investigation to establish the cause. The details of an approach to investigating AEFI clusters are described later.

The symptoms arising from an immunization error may also help to identify the likely cause. For instance, children immunized with contaminated vaccine (usually the bacterium *Staphylococcus aureus*) may 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 aluminum-containing vaccines, especially DTP. They, along with other local reactions, are more likely to occur if there is inadequate shaking of the vaccine before use, superficial injection and use of 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 as an immunization error. The immunization team should be clearly aware of such contraindications and any precautions. As stated earlier, precautions are not contraindications and uncertainty should be referred to a higher level – a programme manager or a designated IVD staff, pediatrician or physician. Generally, 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. 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.

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

a) It is both important and necessary to maintain the cold chain at all levels.

b) Vaccines must be reconstituted only with the diluents supplied by the manufacturer.

c) Reconstituted vaccine should be maintained in the recommended cold chain and used within six hours after reconstitution; and must be discarded at the end of each immunization session and should never be retained.

d) Other than vaccines, no other drugs or substances should be stored in the refrigerator of the immunization center.

e) Immunization workers must be adequately trained for the use of the vaccines, infection and control measures and should be closely supervised to ensure that proper procedures are followed throughout vaccination session.

f) Epidemiological investigation of each serious AEFI is needed to identify the cause and to correct immunization practices.

g) Prior to immunization, adequate attention must be given to contraindications.

h) Standard operating procedures (SOPs) for all essential immunization procedures such as SOP for waste disposal.

i) Training for the management of possible AEFIs

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.

Normally, high rates of immunization error-related reactions are anticipated when vaccines, especially newly introduced vaccines such as COVID-19 are administered on a massive scale in a short time interval, especially with minimal training and field preparation.

To prevent immunization error-related reactions in mass immunization campaigns, specific training of HCWs is needed and processes for safe vaccine administration and waste disposal should be thoroughly implemented. Before vaccinating, HCWs should verify the product information on vaccine and diluent vial labels, check for vaccine contraindications, as indicated in the product information leaflet.

2.4.11.1 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 type of AEFI is referred to as immunization anxiety-related reaction or “immunization stress-related response” (ISRR). Immunization anxiety-related reactions 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 ISRR. 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 vaccines is 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 judgement are necessary to differentiate between anaphylaxis and ISRR (**Table 6**).

For COVID-19 vaccination, a larger number of Immunization anxiety-related reactions may be resulted from numerous factors including different vaccination groups eg., the different

vaccination environments, the novelty of the vaccines and the difference in administration modalities all may trigger anxiety related reactions.

Table 6: Differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope

ACUTE STRESS RESPONSE

	ANAPHYLAXIS	GENERAL	VASOVAGAL REACTIONWITH SYNCOPE
Onset	Usually occurs 5 min after immunization but may be delayed up to 60 min	Sudden, onset occurs before, during or shortly after (< 5 min) immunization	Sudden, onset occurs before, during or shortly after (< 5 min) immunization. May present after 5 min if the individual stands suddenly.
System			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle sensation, localized injection site urticaria, red and itchy eyes	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.	Hyperventilation (rapid, deep breathing)	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ blood pressure, circulatory arrest	↑heart rate, normal or ↑systolic blood pressure	↓ heart rate with or without transient ↓in blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat	Fearfulness, light headedness dizziness, numbness, weakness, tingling around the lips, spasms in hands,	Transient loss of consciousness, good response once supine or lying flat, with or without tonic–clonic

	ANAPHYLAXIS	GENERAL	VASOVAGAL REACTIONWITH SYNCOPE
		feet	seizure

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. Sometimes, 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 judgement to differentiate between anaphylaxis and syncope is necessary.

2.4.12 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. Childhood 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. The same also applies in elderly individuals receiving COVID-19 vaccines who might have other comorbid conditions which may be falsely perceived as vaccine related reactions.

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.

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.

3.0 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is a pre-specified medically-significant event that has the potential to be causally associated with a vaccine product but needs to be carefully monitored and confirmed by further special studies. AESI may be serious or non-serious and they warrant further investigation in order to characterize and understand them.

AESI are usually identified through active vaccine safety surveillance (AVSS) systems. Conditions commonly considered as AESIs include serious events that have followed other immunizations, for example:

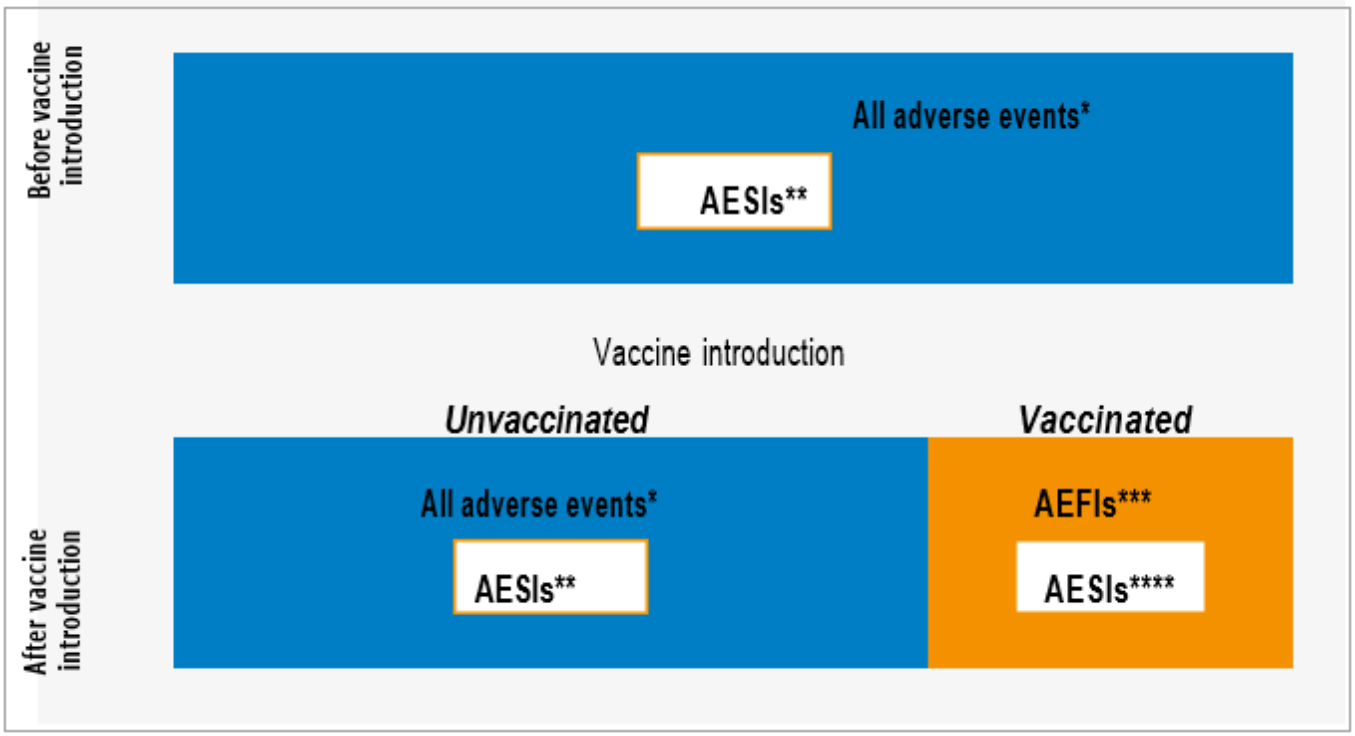
a) Guillain-Barré syndrome (GBS);
b) acute disseminated encephalomyelitis (ADEM);
c) anaphylaxis;
d) serious events potentially related to novel platforms;
e) serious events potentially related to adjuvants;
f) serious events related to vaccine failure/immunogenicity (vaccine-associated enhanced disease (VAED)); or
g) events that are potentially important for specific populations.

Such conditions are shortlisted if there is a:

a) proven association with immunization that is true for most, if not all, vaccines;
b) proven association with a known vaccine platform or adjuvant that is being used in any COVID-19 vaccine;
c) theoretical concern based on immunopathogenesis of COVID-19 disease;
d) theoretical concern related to viral replication during COVID-19 infection; or
e) theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

The relationship between AEFIs and AESIs is shown schematically in **Figure 2** and the difference between AEFIs and AESIs and their practical implications are summarized in **Table 7**

Figure 2: Schematic representation of the relationship between AESIs and AEFIs.



** All events in a community that cause morbidity. Background rates provide information on the incidence of such events in the community*

*** Adverse events of special interest (AESIs) for a community defined prior to COVID-19 vaccine introduction. These events are of 'special interest' because although they are known to occur coincidently in the population, they have the potential to be associated with one or more of the COVID-19 vaccine platforms. It is important to estimate the background rates for these events and set up specific surveillance and training*

**** Adverse events following COVID-19 immunization (AEFIs)*

***** AESIs identified following COVID-19 immunization. In addition to following the requirements for AEFI management, there may be special requirements defined for AESIs, including investigation, follow-up and causality assessment activities*

Table 7: Differences between AEFIs and AESIs and practical implications

	AEFI	AESI
What	Any untoward medical occurrence that follows immunization, and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.	A pre-specified event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.
Purpose of collecting information	To identify all events after vaccination – determine if serious, investigate (serious) and do causality assessment.	To identify pre-specified specific events by a set criterion and determine if the event is associated with vaccination.

	AEFI	AESI
Identification method	Identified via spontaneous reporting by vaccine recipients or their parents, or health care workers or other persons who first notice the event.	Identified via an active surveillance system in sentinel sites or electronic health record (EHR-based cohort studies, Case Control studies, Self-Controlled Cohort Studies, rapid assessment by a health care worker or other staff in the system.
Case definitions	Important	Critical
Type of reporting	All events that follow immunization and are notified to the health care system.	All events identified through active surveillance that fit the case definition, irrespective of immunization status.
Training	All frontline immunization staff in health care facilities (public and private); and other relevant staff for reporting, investigation, data analysis, and causality assessment	Immunization staff and other health care workers in sentinel sites and predefined active surveillance systems, IVD, research institutions, AEFI Committee
Users	Health care workers, IVD, TMDA, surveillance and information managers, epidemiologists, surveillance and information managers, vaccine safety partners including the community	Sentinel site staff, IVD, TMDA, epidemiologists, national AEFI committees, study teams.

Shortlisting pre-specified AESIs before introduction of a new vaccine enables preparation for vaccine safety surveillance. This will involve defining the events, ensuring suitable tools are available to detect them, providing training for relevant staff and identifying the disease codes and estimating the background rates for the AESIs. This is important because AESIs are generally detected and reported through active vaccine safety surveillance (AVSS) systems.

4.0 AEFI SURVEILLANCE IN TANZANIA

4.1 Objective of Surveillance of AEFI in Tanzania

Surveillance of adverse events following immunization (AEFI) is an integral part of IVD and TMDA. Safety surveillance reinforces safe use of all vaccines in the country while also helps to maintain the confidence of the community and health staff in the immunization program by providing appropriate and timely responses to their concerns about immunization safety.

Surveillance system of AEFI in Tanzania is conducted mainly through passive (spontaneous) surveillance whereby AEFI are spontaneously reported from immunization service providers/hospitals/patients to TMDA through the reporting system. Other surveillance systems such as active surveillance and ad-hoc (epidemiological) studies are recognized and maybe used when necessary and logistically possible.

The primary purpose of AEFI surveillance is to identify and respond to events that are temporally associated with immunization. In Tanzania, the AEFI surveillance is conducted systematically (**Figure 3**) and has the following objectives: -

To detect and identify problems with vaccines which could be due to the inherent properties of a vaccine or to defects in quality. Also, responding timely and accordingly and thus, maintain the confidence of the community and health staff in the immunization programme.

To detect, correct and prevent immunization error-related reactions;

To determine the observed reaction rate and relate this to the expected vaccine reaction rates in the population by region, country or globally;

to create awareness on immunization safety among parents, community, the media and other stakeholders without jeopardizing the immunization programme;

Figure 3: AEFI surveillance cycle

Generating information with which to effectively communicate with parents, the community, media and other stake holders, regarding the safety of vaccines used in Tanzania;

To ensure that coincidental reactions events are not mistaken for vaccine reactions thus negatively affect the immunization program;

To ensure and facilitate causality assessment of individual AEFI reports (cases);

To identify clustering or unusually high rates of AEFI, even if they are considered mild;

to identify events which may indicate a previously unknown and potential vaccine reaction (i.e. a signal) and to generate new hypotheses about the causal relationship between the event and the vaccine (this will then require further investigations to support or refute the hypothesis);

To ensure that channels of communication on AEFI between TMDA and IVD are clear and that information is provided regularly;

To collaborate and share information with the WHO regional offices and globally in order to generate additional information on vaccine safety

4.2 AEFI Reporting and case definitions

In Tanzania, the reportable AEFI are: -

a) Serious AEFI;
b) Signals and events associated with a newly introduced vaccine;
c) AEFI that may have been caused by an immunization error;
d) Significant events of unexplained cause occurring within 30 days after vaccination;and
e) Minor events causing significant parental, healthcare worker or community concern.

It is worth emphasizing that primary reporter is not expected to assess causality and therefore even a suspicion alone is warrants reporting.

Minor AEFI such as high fever and local reactions causing parental, healthcare-worker or community concern should also be reported even though they are expected reactions to vaccines. Reporting and monitor these events helps to compare the crude number of these events with the background rates that could identify product quality defects, immunization errors or even increased susceptibility of vaccine reactions among a particular population. **Table 8** below provides case definitions of some commonly reportable AEFI. It is important to note that the list is not exhaustive and the time interval between immunization and onset of the event may not always be precise or well established. For more case examples and diagnostic certainty of case definitions please refer to the Brighton Collaboration.

Table 8: List of examples of reportable AEFI and their case definitions

Reportable AEFI	Time onset following immunization*
Acute flaccid paralysis for OPV recipient Acute flaccid paralysis for contact of OPV recipient	4-30 days following immunization 4-75 days following immunization
Anaphylaxis (after any vaccine)	Within 48 hours of immunization
Brachial neuritis (after tetanus-containing vaccine)	2-28 days following immunization
Disseminated BCG infection after BCG vaccine	Between 1 and 12 months
Encephalopathy after measles/MMR vaccine after DTP vaccine	 6-12 days following immunization 0-2 days following immunization
Hypotonic hyporesponsive episode (HHE) after	Median time is 3-4 hours but ranges

Reportable AEFI	Time onset following immunization*
DTP/PVV vaccine	
Injection site abscess (bacterial/sterile) after any injectable vaccine	Not specific. However, commonly within first 14 days of immunization
Intussusception (after rotavirus vaccines)	Commonly within 21 days, risk increased after the first 7 days and usually first dose
Lymphadenitis after BCG vaccine Osteitis/osteomyelitis after BCG vaccine	Between 1 and 12 months
Persistent (more than 3 hours) inconsolable screaming after DTP/PVV vaccine	Common immediately and up to 48 hours of immunization. However, it can occur even after 48 hours
Sepsis (after any injectable vaccine)	Within 7 days following immunization
Seizures, including febrile seizures after measles/MMR after DTP/PVV	 6-12 days following immunization 0-2 days following immunization
Severe local reaction (after any injectable vaccine)	Within 7 days following immunization
Thrombocytopaenia (after measles/MMR)	Median time is 12-25 days after immunization, but the range is 1-83 days
Toxic shock syndrome (TSS) (after any injectable vaccine)	Commonly within 72 hours following immunization
Death Hospitalization Disability Any other severe and unusual events that are attributed to immunization by health workers or the public	No time limit, but in general those within 30 days following any immunization

*The time interval to onset will depend on the antigen and the adverse reaction. For detailed information on antigen or adverse reaction-specific onset intervals, refer to the Brighton Collaboration case definitions (https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html), WHO position papers and observed rates information sheets (https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/reaction-rates-information-sheets l ,

4.3 When to report

Reporting should be done immediately, as soon as an AEFI is detected. Rapid detection and evaluation of a possible link between AEFIs and vaccines is essential to ensure the continued safety of vaccines. AEFI report must be made as quickly as possible so that an immediate decision can be made on the need for action and investigation.

In case of a serious event, excess number of cases or case(s) causing a high level of community concern, an alert should be sent by the quickest means possible including telephone, email, SMS etc., to the next decision- making administrative/operational level including national level (TMDA/IVD).

4.4 How to Report

AEFI cases should be reported using standard AEFI reporting form **(Annex 1).** Both paper-based and electronic reporting formats are available. It is the responsibility of the TMDA zonal offices in collaboration with the District Pharmacist (DPharm) to ensure that all facilities including hospitals, health centers, dispensary and drug dispensing outlets have sufficient reporting forms or access to the electronic reporting system.

All healthcare workers in a healthcare system have the responsibility of reporting AEFI. When reporting for AEFI, it is essential that all the minimum required information is entered into the reporting form, as this is the basis for decisions regarding the need for further investigation.

A limited number of variables are required to manage AEFI information properly. These are known as 25 core variables for AEFI reporting **(Table 9).** These include a unique identifier for the report, the primary source of information, patient characteristics, details of the event(s), vaccine(s) of interest, and the possibility of collecting additional information if needed. Any additional information that is collected would be useful for investigation.

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

Description	Core variable	Terminology used in the AEFI reporting form	Description of the Basic core variable
Record Identifier	1	Date AEFI report first received at National level (TMDA or IVD)	Date when information of the AEFI case first reached the National level (IVD or TMDA)
	2	Health facility (or vaccination center) name	Geographic location of the place where recipient got vaccinated
	3	Reporter address	The name of the country where the data is first entered
	4	Patient's full address	Geographic location of the patient
	5	AEFI worldwide unique ID	Unique number used for communicating the details of the case at the international level
Patient	6	Patient name or initials	The name of the patient or initials
	7	Date of birth	Date patient was born
	7	Age at onset	If date of birth is not known, this should be considered as first alternative
	7	Age Group	If date of birth and age at onset is not known, this should be considered as second alternative
	8	Sex	Male or Female
	9	Describe AEFI (Signs and symptoms):	Describe signs and symptoms of AEFI including sequence and progression as seen by the reporting HCW and also as described by the patient/caretaker
Vaccine	10	Generic name of the suspected vaccine	Generic name of the vaccine (eg., measles, BCG or COVID-19) that is suspected to have caused the AEFI
	10	Brand name including the manufacturer's name of suspected vaccine	The vaccine that is suspected to have caused the AEFI (brand name)

Description	Core variable	Terminology used in the AEFI reporting form	Description of the Basic core variable
	11	Other vaccines	Other vaccines given prior to the onset of AEFI
	12	Batch/ Lot number	Batch number/lot number of each of the vaccines mentioned above
	13	Dose (1st, 2nd, 3rd etc.)	The dose number for the vaccine
	14	Diluent Batch/ Lot number	Batch number/lot number of the diluent that was actually used (if applicable)
Event	15	Date & Time of vaccination	Date and time when the vaccine was administered
	16	Date & Time AEFI started	Date and time the event was first identified by/ in the recipient
	17	Adverse Event(s)	The case diagnosis + signs and symptoms
	18	Outcome of AEFI	Indicate status of the patient at the time of reporting: Recovering, Recovered, Recovered with sequelae, Not Recovered, Unknown or Died
	19	Seriousness	If the event resulted in death, threatened the patient's life, caused disability, hospitalization or congenital anomaly, or any other medically relevant event that may jeopardize the patient's health or may require intervention to prevent one of the outcomes mentioned here
Reporter	20	AEFI reporter's name	Name of person who has reported this AEFI to the healthcare system and also completed this form
	21	Institution/location	The place where the reporter is working or is affiliated to
	22	Designation and Department	Reporter's designation and department
	23	Telephone & e-mail	Telephone and email address of the reporter
	24	Reporting date (today's date)	Date when the report was compiled by the reporter
Other	25	Comments (if any)	Additional details about the case in free text (including documents/ attachments such as laboratory investigation forms and investigation forms as applicable)

Health care providers also have the additional responsibility to manage AEFI in line with the applicable treatment guidelines and, if necessary, refer such patients for further treatment as maybe indicated.

Serious AEFI cases should be notified to the District Pharmacist (DPharm) by telephone as soon as the healthcare facility becomes aware of the event. DPharm has the responsibility of ensuring the completion of AEFI reporting form and informing Regional Health Management Team (RHMT) as well as TMDA/IVD on the occurrence of serious AEFIs in the district. The District Medical Officer (DMO) has the responsibility of initiating investigation of all serious and AEFI clusters in the district. Investigation of cases qualifying for investigation should be initiated within 48 hours of its occurrence. Reporting forms for serious AEFI cases should be immediately entered in the Vigiflow database and e-mailed to TMDA/IVD and the regional level for notification even before completion of all aspects of an investigation. For all AEFI cases, the DPharm will collaborate with the District Immunization and Vaccination Officer (DIVO) and share the District level AEFI cases (linelisting).

4.5 Reporting AEFI during immunization campaigns

A campaign is an opportunity to strengthen or establish immunization safety surveillance through mass immunization and special immunization programmes. Compared to routine immunization, mass immunization and special immunization programmes cover a large number of individuals in a particular target group in a specified, usually short period.

During these special immunization programmes, a new vaccine may be introduced with no prior experience of, or little information on AEFI. Therefore, there is a possibility of detection of signals through strengthening surveillance. Also, an excess number of adverse events may be reported within a short time period. Therefore, unless an event is properly investigated, analyzed and rightly communicated, it can significantly cause concern among the public and with potential to negatively affect the immunization programme.

Proper planning and preparation prior to the immunization campaign is essential for effective safety monitoring of vaccines. This helps to significantly reduce occurrence of immunization error-related reactions, allows taking immediate and coordinated actions and limit the potential for negative publicity from an AEFI. Planning also includes sufficient training to the vaccination teams on safety monitoring of vaccines, proper immunization practices, storage of vaccines, potential AEFI and reporting as well as refresher training on investigation of AEFI cases.

During immunization campaign it is essential to designate an overall focal person who will be responsible for coordination of all AEFI related issues during the campaign. The focal person will be assisted by team leaders who will ensure each vaccination team has sufficient reporting tools including job aids and alert the overall coordinator on the occurrence of AEFI within in the team.

Regional/district immunization and vaccine officers should also work closely with AEFI designated team/focal person throughout the campaign. When needed, regional teams will provide support to the district teams to ensure that investigations are initiated within 48 hours upon notification and reports submitted to TMDA/IVD for causality assessment by the AEFI Vigilance Committee (AEFI Vigilance Technical Committee).

5.0 ROLES AND RESPOSIBILITIES OF STAKEHOLDERS

5.1 Subnational Stakeholders

Subnational stakeholders in AEFI reporting and investigation are;

a) Vaccine recipients and community;
b) Healthcare workers;
c) District Pharmacist (District Pharmacovigilance Focal Person);
d) District Immunization and Vaccine Officer (DIVO);
e) Regional Immunization and Vaccine Officer (RIVO); and
f) Regional Pharmacovigilance Focal Person

5.2 National stakeholders

National stakeholders are;

a) IVD Programme
b) TMDA
c) National AEFI committee embedded within National Vigilance Technical Committee (VTC)

5.3 Role of Sub national level stakeholders

5.3.1.1 Role of the health worker

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 therefore notified to any health care provider working within the health care system, should be reported using the standard reporting form (**Annex 1**).

In charge of the healthcare facility should supervise and ensure smooth operation of AEFI surveillance activities at the facility level. This includes ensuring availability of AEFI reporting forms, ensuring completeness and accuracy of the filled forms and proper archiving of AEFI forms. Also, in charge of the facility has the responsibility of timely notifying DIVO/DPharm and to participate in the investigation of eligible AEFI cases by filling AEFI investigation form (**Annex 2**).

As outlined earlier, the main role of the health worker is to provide primary medical care and report the basic details about the patient and the adverse event to the district by completing the AEFI reporting form (preceded if appropriate with a preliminary report by telephone in case of a serious event).

5.3.1.2 Role of stakeholders at the council and regional level

When an AEFI report is received by the DPharm, s/he must ensure that details of each case, irrespective of whether it is a minor or serious AEFI have been entered in the district linelist of AEFIs maintained at the DIVOs or DPharm office **(Annex 3)**. DIVO/DPharm should review

the report and determine if the reported AEFI case meets the criteria required for a detailed investigation. DIVO/DPharm should immediately inform the respective DMO who will initiate the investigation of AEFI case(s) by filling AEFI investigation form **(Annex 4).**

For minor and non-severe AEFI cases warranting no detailed investigation, s/he should indicate this on the reporting form, update the linelisting and enter in the Vigiflow or send the same to the regional or TMDA zonal for Vigiflow entry and archiving.

In addition to reporting and investigating cases of AEFI, regional (RHMT) and district (CHMT) stakeholders have the responsibility of taking corrective and preventive actions. For example, if any immunization error-related reactions are observed, preventive actions such as strengthening supportive supervision, training and even logistic replacements should be implemented by authorities at this level. Also, sub-national stakeholders have a responsibility of monitoring, supervising and training on key functions of AEFI surveillance at their level.

5.3.1.3 Role of the National stakeholders

When the IVD/TMDA receives the AEFI report, 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 with information from the reporting form and reviewing the data or running analyses as needed. The national line list of AEFI will be updated monthly as reports are received from the sub-national levels. 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 National AEFI Committee is embedded within the National Pharmacovigilance Committee.

The TMDA 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 Tanzania National Immunization Technical Advisory Group (TITAG) and the MoH on vaccines based on their causality assessment findings. The TMDA and the IVD Programme together constitute the secretariat team to the National AEFI Committee and therefore they coordinate and provide technical/logistical support to the Committee meetings.

National level stakeholders (IVD/TMDA) are also responsible for providing feedback to the relevant stakeholders at the regional and district level 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 level and regional level (e.g. change in logistics, cold chain, training after program errors etc.) and ensuring that they are implemented.

The TMDA as the national pharmacovigilance center is responsible to upload the information into the Global pharmacovigilance database – Vigiflow®, maintained by the Uppsala Monitoring Centre under the WHO International Drug Monitoring Program – using information available in the completed case investigation form. A copy of the uploaded case details in Vigiflow® should be provided to IVD Tanzania on a monthly basis. The TMDA can also provide information on the vaccines and lots distributed in the country when requested by the

AEFI committee, IVD Programme and the Tanzania National Immunization Technical Advisory Group (TITAG). TMDA can also provide additional information on AEFI from other sources.

The timelines for communicating AEFI between stakeholders at all levels have been summarized in **Figure 4** of this document.

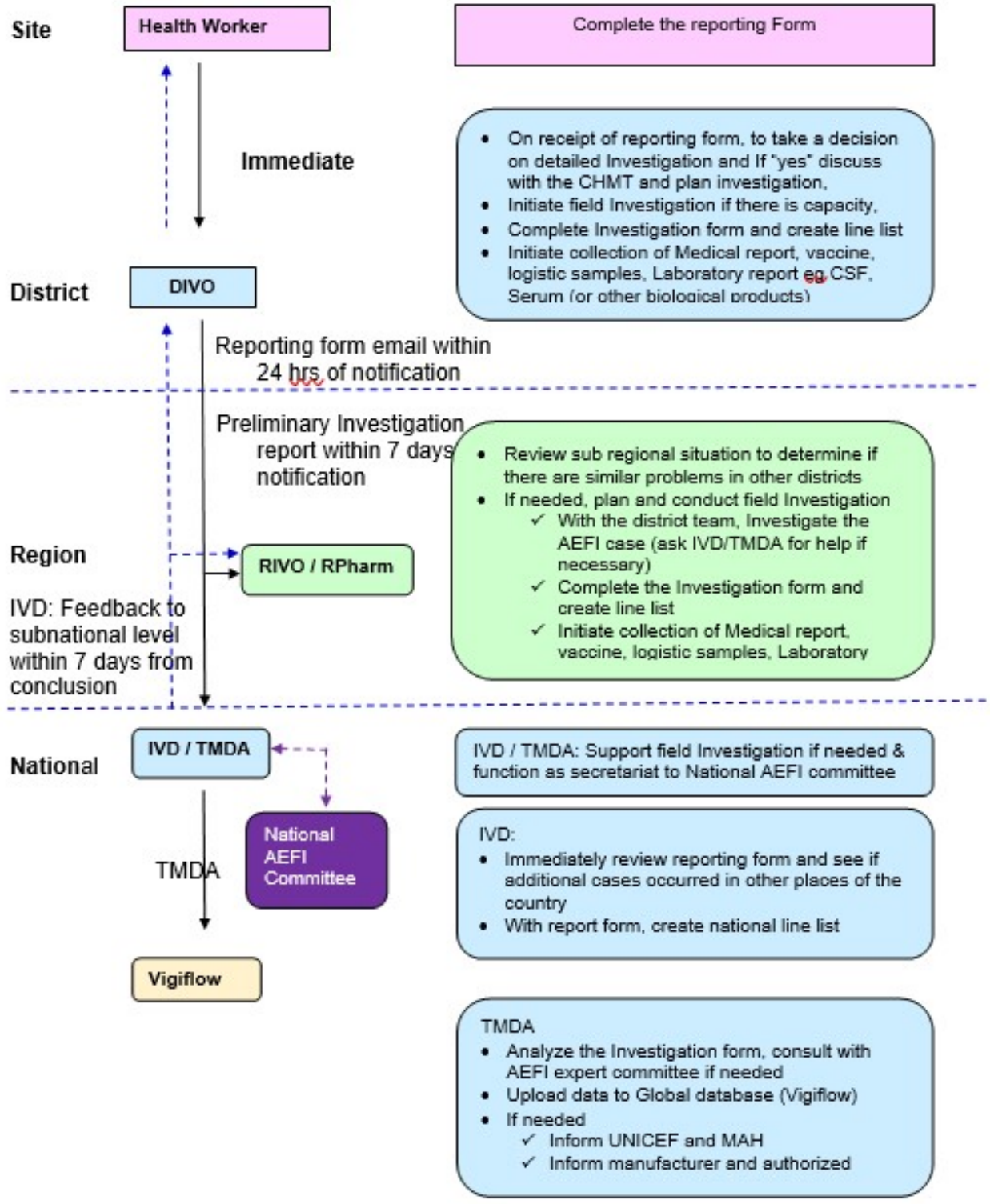


Figure 4: Tanzania AEFI Reporting – Routing, Timeline and Actions

6.0 INVESTIGATION OF AEFI CASES

6.1 The purpose of Investigation

The ultimate goal of investigation of AEFI cases is to systematically examine the reported serious adverse events following immunization (AEFI) and ascertain the underlying cause and implement follow-up actions. Investigation should identify any immunization error-related or vaccine product-related reactions because these are preventable. If coincidental events are recognized, proving them will be important to maintain public confidence in the immunization programme.

The purposes of investigating an AEFI case are the following:

a) To identify the details of vaccine(s) administered and to determine the timing between administration of the vaccine and the onset of the event;

b) To confirm the reported diagnosis or establish a diagnosis;

c) To document the outcome of the reported adverse event;

d) To identify the cause of the AEFI;

e) To determine whether a reported event is a single incident or part of a cluster and, if it is part of a cluster, where the suspected immunizations were given and what vaccines were used;

f) To examine the operational aspects of the programme (even if an event seems to be vaccine-induced or coincidental, immunization-related errors may have increased its severity) and to prevent immunization-related errors; and

g) To determine whether similar events are occurring in individuals who have not received the same vaccine.

During field investigations, 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.

6.2 Selection of AEFI cases for investigation

The following AEFI must be investigated, if it:

a) Appears to be a serious event (that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect) of known or unknown cause;

b) Belongs to a cluster of AEFI;

c) Is a previously unrecognized event associated with an old or newly introduced vaccine;

d) Involves an increased number or rates of known cause;

e) Is a suspected immunization error;

f) Appears on the list of events defined for AEFI surveillance; and

g) causes significant parental or public concern.

6.3 Composition of AEFI Investigation team

The District Medical Officer or a designated medical officer in charge (MOI) of the facility shall be responsible for forming an investigation team. The profile of investigators who carry out detailed AEFI field investigation will be determined by the operational structure and the expertise available to the surveillance system in the respective district or facility. For many cases, especially if the cause of the reported is very clear, investigation of AEFI can be effectively conducted by the responsible healthcare workers at the facility/district level with no need of an addition of expertise from the region or national level (TMDA/IVD). For some intricate cases, investigation should be done by next/higher administrative level, by a trained/skilled person/ team, depending on the nature of event, its seriousness and impact to the program.

Even in such circumstances, in which the capacity to conduct comprehensive investigation is not available at the district or regional level, collection of preliminary information on detailed investigations is still the responsibility of the subnational level. Therefore, having a plan for responding to serious AEFI requires regions and district to have identified adequate expertise tailored to its particular circumstances.

Ideally at the facility level the team should be composed of a medical doctor(s), health facility in charge, a staff from Reproductive and Child Health (RCH) department and a pharmacist or drug store keeper. At minimum, the district investigation team should be composed of a medical doctor, DIVO and DPharm. It is important for investigators to be well conversant with vaccination activities and overall conduct of investigation for serious and cluster events.

As a coordinating office of vigilance and other regulatory activities at the zonal level, TMDA zonal offices have the responsibility of supporting districts and the respective regions in conducting investigation of AEFI cases. Through TMDA zonal manager, TMDA zonal offices should support subnational teams and ensure that facilities and districts are timely investigating all cases that meet investigation criteria and reports are submitted to the national level.

6.4 Timelines for investigation of AEFI

Investigation of cases that meet criteria for investigation, should be conducted as soon as possible. Investigation should be initiated within 48 hours upon notification of the healthcare worker at the facility level. This is in order to determine the cause, identify additional cases and prevent the occurrence of more cases through institution of effective intervention measures.

Preliminary investigation reports containing investigation form, case sheets, discharge summary, case notes, laboratory reports and autopsy where available, should be shared to the regional and national level within seven (7) days of notification. Facilities, districts and regions should not wait until all documents become available before sharing to the regional and national level. When appropriately filled, investigation form, AEFI reporting form as well as case notes may sufficiently provide adequate information to provide initial understanding on the link between the reported AEFI case and the vaccine given.

6.5 Steps in conducting AEFI investigation

a) The specific activities conducted at this point will include the following.

b) 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);

c) Convene a Council Health Management Teams (CHMT) planning meeting prior to the investigation;

d) With the members of CHMT, the investigation team should visit as required the patient, the care provider(s) and the hospital; interview relevant stakeholders (parents, health worker, treating doctor, vaccine supply focal person); and conduct the investigation of the AEFI case.

e) Complete the AEFI investigation form; and

f) Initiate collection of medical reports, a post-mortem report (if available), vaccine vials (if necessary, and kept under cold chain conditions), logistic samples, and laboratory reports e.g., Cerebral Spinal Fluid (CSF), Serum (or other biological products).

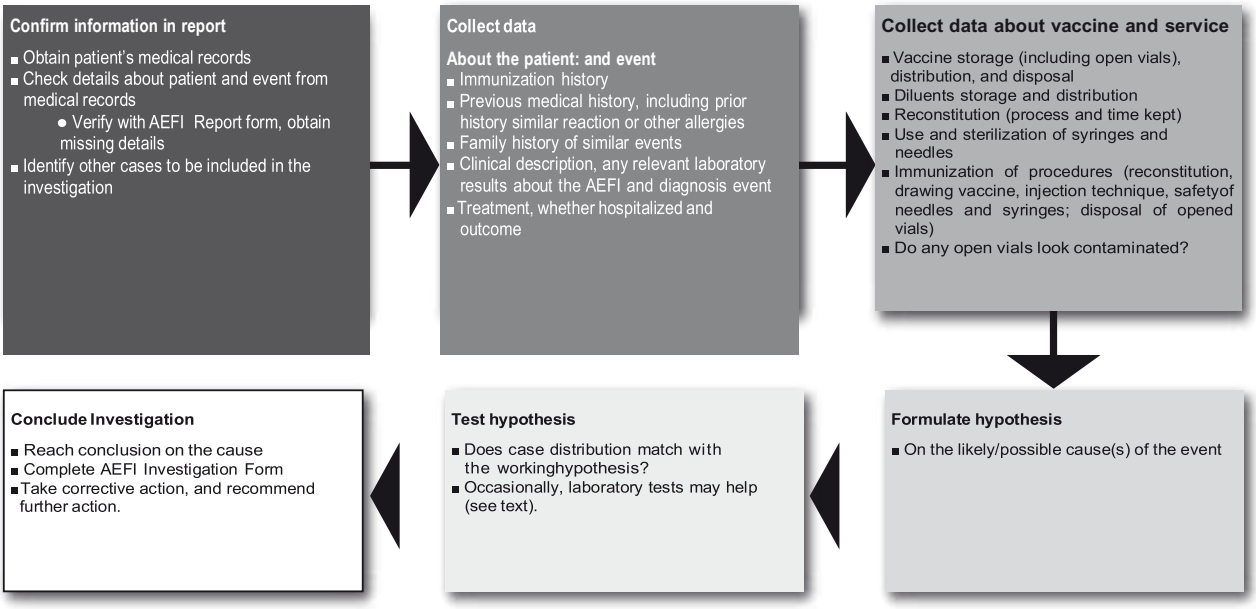


Figure 5: Steps in AEFI Investigation

An AEFI investigation follows standard principles of epidemiologic investigation **(Figure 5).** It is important to investigate suspected adverse events promptly and completely. The investigator will primarily need to focus on the reported reaction as well as gather information from the patient/parent, health workers and supervisors, and community members. The information collected (and conclusions) should be systematically recorded on an AEFI investigation form **(Annex 2).**

Generally, immunization error-related events and coincidental events are the commonest AEFIs. Therefore, before the AEFI is attributed to any vaccine product related problems, investigators should rule out any potential immunization errors and obvious coincidental events. 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.

Overarching goal of an investigation is to identify the system problems rather than blaming individuals. For example, if an investigation reveals that most abscesses are reported from one immunization clinic due to the faulty immunization technique of a health-care worker, rather than blaming the particular worker, the investigators should endeavor to find reasons why that health-care worker uses the incorrect technique. The underlying cause could be due to a system failure such as lack of training or lack of supportive supervision and this should be promptly addressed.

Once the investigation has been initiated, the District/Regional investigator should inform IVD and TMDA on the status and progress of the investigation. This is necessary, as a national level officer should be the spokesperson of the government to the media and the public about the investigation. The completed case investigation form along with the supporting documents such as the medical report, vaccine, logistic samples, laboratory reports e.g., Cerebral Spinal Fluid (CSF), Serum (or other biological products) should be sent to the IVD/ TMDA within 7 days of initial case notification. If this is not possible, at least a progress report should be made available 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 joint investigation rather than a piecemeal investigation. **Table 10** summarizes the key steps in AEFI investigation of AEFI cases.

Table 10: Steps in investigation of AEFI cases

No.	Step	Actions
1	**Confirm** information in report	Obtain patient's medical file (or other clinical record) and AEFI reporting form Check details about patient and event from AEFI reporting form and other medical records available. Obtain and document any details missing from the AEFI report form. Identify any other cases that need to be included in the investigation
2	**Investigate** and collect data: About the **patient's**	Immunization history 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 of autodisable syringes and needles Number of immunizations (greater than normal?) Details of training in immunization practice, supervision and vaccinator(s).
	Observe the service in action:	Refrigerator – what else is stored (note if similar containers stored next to vaccine vials which could be confused); which vaccine/diluents stored with other drugs; whether any vials have

No.	Step	Actions
		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	Compile all the relevant documents including information from the local area, health facility reports, field reports, hospital records, laboratory results, autopsy reports and results of any tests conducted Does case distribution match the working hypothesis? Laboratory tests may help (see text).
6	**Conclude** investigation	Reach a conclusion on the cause. Complete AEFI Investigation Form **(Annex 2)** Transmit investigation report to the next higher level Take corrective action, and recommend further action

In the event of an identified death following immunization, field investigation has to be initiated without a delay as the death can cause significant community concern. Within 24 hours the death event should be notified to all administrative levels concerned, including DIVO, RIVO, IVD Programme and TMDA. Investigation of the case should be carried out by a team of experts from relevant areas including clinicians and laboratory experts. Since a death which is causally linked to immunization is extremely rare (anaphylactic reactions being one of the only 2-3 known events), major programmatic errors may be involved and thus an investigation to rule those out has to be conducted without any delay to prevent further cases. As any fatality temporally linked to a vaccination can cause panic, the public will also demand an immediate explanation.

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

6.6 Investigating AEFI clusters

A cluster of AEFI is defined as two or more cases of the same adverse event related in time, place or vaccine administration. Apart from checking on these three factors, the investigator should look for AEFI occurring in similar age groups and populations with genetic predisposition or disease. Investigation of cluster begins by establishing a case definition for the AEFI and related circumstances and by identifying all cases that meet the case definition.

The investigator 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 information on: -

a) Detailed data on each patient;
b) Programme-related data (storage and handling, etc.); and

c) Immunization practices and the relevant health workers' practices.

Common exposures among the cases can be identified by reviewing:
a) All data on vaccine(s) used (name, lot number, etc.);
b) Data on other people in the area (also non-exposed); and
c) 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 **(Figure 6).** Usually the key considerations will be to investigate the possibility of an immunization error vaccine or a 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 programmes targeting adolescent girls.

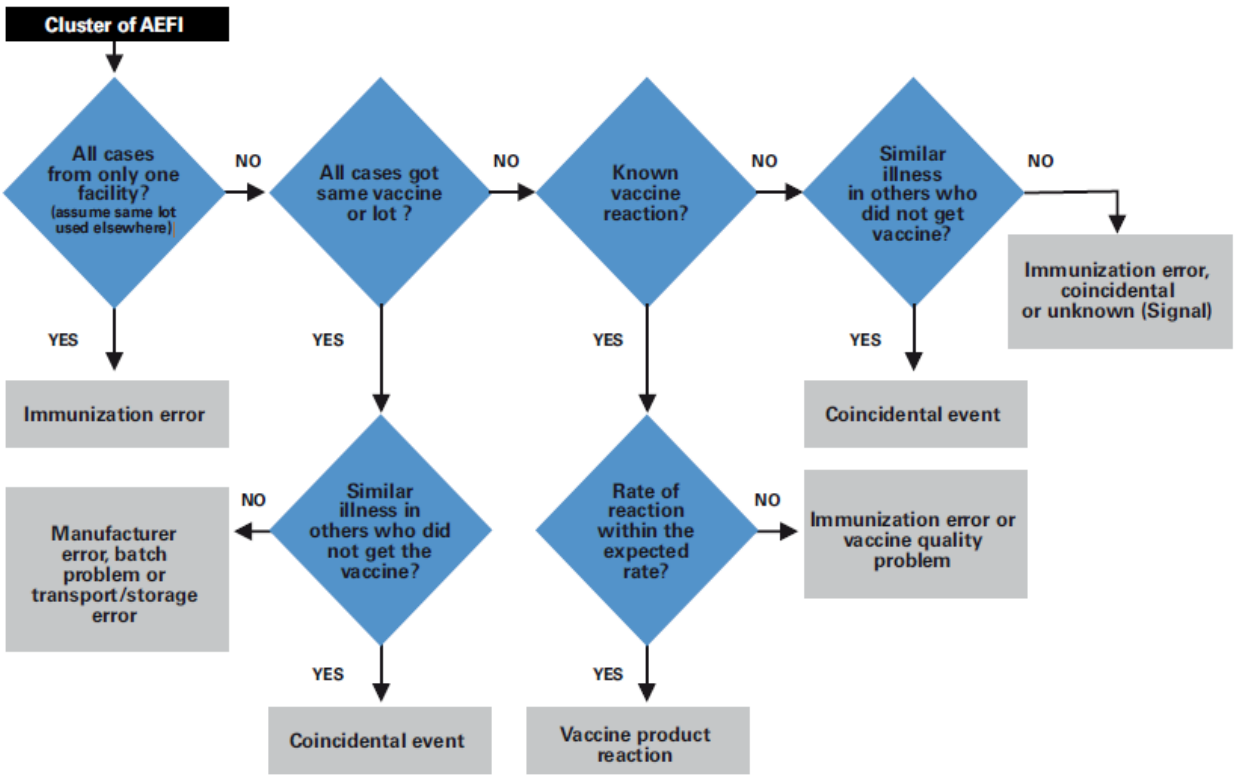


Figure 6: Identifying the causes of an AEFI cluster

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.

6.7 Interpretation of results from AEFI clusters

If all cases received vaccines from the same health worker/facility and there are no other cases, an immunization error is likely. If all cases received the same vaccine or lot, and there are no similar cases in the community, a problem with the vaccine or the respective lot is likely. If the

event is a known vaccine reaction but is found to occur at an increased rate, an immunization error or a vaccine problem are likely causes. Finally, if cases in the unvaccinated population are occurring at about the same rate/proportion as among the vaccinated from the same area in the same age group, the adverse event was probably coincidental **(Table 11).**

In a cluster analysis, if a previously unknown event is reported only among the vaccinated group, it can be a potential signal provided that both immunization error-related reactions and coincidental events are excluded. Such AEFI require comprehensive assessment and further studies to understand their true causality **(Figure 6).**

Table 11: Cause-specific cluster characteristics

Cause Specific	Cluster Characteristics
Vaccine reaction (product-related or quality defect- related)	If all cases received the same vaccine or lot, and there are no similar cases in the community If an increased frequency of events is reported from multiple settings
Immunization error- related	If all cases received vaccines from the same health worker/facility and there are no other cases
Coincidental	If cases include people from the same area in the sameage group who were not immunized
Immunization anxiety-related	Clusters of fainting after immunization are well-reaction recognized as anxiety-related reactions during

7.0 LABORATORY TESTING OF SPECIMENS

Laboratory testing may sometimes confirm or exclude the suspected cause. However, testing should be requested on the basis of clear suspicion and not as a routine procedure, and never before the working hypothesis has been formulated. Determination of which samples to test, if any, should be guided by the working hypothesis.

7.1 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 doctor in charge of the case. **Table 12** 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 decide on samples to be tested.

For biochemical, histopathological and microbiological examination, specimens should be handled at the district or regional hospital 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 (Region/District) institutions, sending samples to national laboratory or an accredited laboratory abroad need to be considered after discussing with IVD/TMDA.

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 laboratories identified by IVD/TMDA 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.

7.2 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 laboratories are outlined in **Table 12**.

Table 12: Human specimen and the type of tests to be performed

Suspected AEFI	Diagnostic Method	Specimen	When to collect	Preparation, Storage and shipment	Referral of Specimens
Injection site abscesses	Microscopy and Culture/ sensitivity	Pus Swab	At contact	Use Transport media to transport pus swabs to the next level	Next Level with Culture and Sensitivity Facilities
BCG lymphadenitis	Microscopy , Culture and serology	Blood, LN Aspirate or Biopsy and	At Contact	Wrap in leak proof and water proof container transport.	Regional and National Public Health Laboratory (NPHL) and

Suspected AEFI	Diagnostic Method	Specimen	When to collect	Preparation, Storage and shipment	Referral of Specimens
		Suspected Vial Batch			TMDA
Collapse or shock-like state	Microscopy, Culture and serology	Blood and Suspected Vial Batch	At Con-Tact	Blood smear Blood sugar tests at site Ensure asepsis for blood collection for culture	District or Regional Hospital Lab (NPHL)
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	District or Regional Hospital Lab or NHLQA-TC
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	District or Regional Hospital laboratory or NHLQA- TC
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	NHLQATC/ TMDA laboratory

Note:

a) Histopathology, body fluids etc. can be done at laboratories identified and approved by the MoH.

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

c) Any vaccine sample requiring testing should be transported in a reverse cold chain

d) Vaccines and diluents for sterility and chemical composition.
e) Syringes and needles for sterility.

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 3) should be completed and sent with any specimen collected.

- Laboratory testing is not a routine requirement but may be a part of an investigation.
- Laboratory testing is costly and is recommended only when it is necessary.
- However, securing samples (vaccine vials, syringes, blood etc.) and storing them correctly is important because later investigation may require them. Therefore, proper storage and transport of suspected samples is recommended.

7.3 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 laboratory for testing only on the recommendation of the CHMTs, RHMT or the Ministry.

Testing of vaccines, diluents and syringes should be requested on a clear suspicion and not as routine and never before the working hypothesis has been formulated (**Table 13**). 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 suspect vaccine is available, it should be sent along with unused vials of the same lot.

The DIVO will be responsible for the packaging, cold chain maintenance and shipment of samples in the correct temperature to the national laboratory at TMDA laboratory. All specimens sent to the laboratory should be accompanied with a laboratory request form (Annex 3).

The testing laboratory will process the specimens and send the laboratory results to National IVD Manager and TMDA Director General. The Laboratory 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.

Table 13: Laboratory testing to investigate AEFI by working hypothesis

Working hypothesis	Specimens to send	Laboratory test
Vaccine transportation or storage	Vaccine vial	Visual test for clarity, presence of foreign matter, turbulence, discoloration or flocculation (examine under magnification)
Reconstitution error	Vaccine vial and/or diluents	Chemical composition analysis for abnormal components (e.g. suspect 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

8.0 DATA AND PERFORMANCE ANALYSIS

8.1 Sources of AEFI data

Information on vaccine safety and the possible occurrence of AEFIs can be obtained from clinical examinations, interviews of health workers, parents and community leaders, review of registers (ANC, OPD and Immunization), vaccine and vaccine supplies ledger, observation of immunization administration, vaccine handling and storage and laboratory reports.

Analysis of data on AEFIs consists of reviewing data from the following sources;

a) Data collated into a line list,
b) Case investigation forms for each reported AEFI case,
c) Laboratory information (Human and vaccine related),
d) Records about similar events in the community,
e) Records of the implicated vaccine.

8.2 Analysis of AEFI reports

It is essential that all notified cases are reported (minor and serious AEFI) using the AEFI reporting form (**Annex 1**). All reported AEFI cases should be line-listed at all levels using the AEFI line-list (**Annex 3**). This is the first step of data management. Before the analysis, verify and reassure the data for accuracy. In addition to basic time, place and person analysis that should be done by the district and regional program managers, other key analysis, some of which also relate to the performance of the surveillance system, include;

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

8.3 Data analysis at different levels

Data analysis could be carried out by the responsible focal persons at different levels in the immunization safety surveillance system:

a) at District level by DIVO and relevant staff

b) at Regional level by RIVO and relevant staff
c) at National level by the IVD and TMDA.

Analysis of data at district level is important to identify the programme errors. This helps to carry out corrective action in a timely manner. **Table 14** describes the type of analysis and the purpose.

Table 14: Types and purpose of data analysis at different levels

Programme implementation level	Suggested Analysis	Purpose of analysis at this level
District level	Number of reports by clinics, hospitals, villages by a given time Reported AEFIs by Place (clinics, hospitals), Persons and time Reported AEFIs by antigen	These are programme operation indicators such as timeliness and completeness Identify immunization errors and thereby will lead to corrective action Will identify vaccine reactions and coincidence
Regional level	Number of reports by district Reported AEFIs by Place (clinics, hospitals), Person and Time Cluster analysis Reported AEFIs by antigen	These are programme operation indicators (timeliness, completeness) at district level Identify immunization (programme) errors and thereby will lead to corrective action. Cluster analysis too lead to identify immunization errors, but also coincidence and vaccine reactions too. Identify vaccine reactions and coincidence.
National level	Number of reports by regions Reported AEFIs by Place (clinics, hospitals), Persons and time Cluster analysis Reported AEFIs by antigen	These are programme operation indicators (timeliness, completeness) at region level Identify immunization (programme) errors and thereby will lead to corrective action. Cluster analysis to identify immunization errors, but also coincidental events and vaccine reactions. Will identify vaccine reactions including signal detection To provide guidance in operational and policy decisions in the country.

8.4 Process of data analysis

Before analysis of the line list at the national level, it is important to re-check the case definitions adopted by the reporting sources. The case should fit into a case definition such as the Brighton collaboration case definitions (www.brightoncollaboration.org) or any definition selected by the National AEFI Committee.

Line lists should be used to sort data by place, person and time. Analysis should be done by antigens by type of reported adverse events (e.g. high fever, abscess) after stratifying data. Number of doses administered for each antigen is the best denominator for calculating reported AEFI rates for each antigen in a given time period (by month, quarter or year). Various denominators and their limitations are described in **Table 15**. Analysis can be expanded to 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 need to be used as the denominator.

Table 15: Selection of denominators and their limitations

Denominator	Limitations
Administered doses of vaccines	Most reliable, may be less accurate
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 under-estimate)

Use of proper multiplier in data analysis is important and also varied by purpose and level of analysis. At local level, percentage (x100= %) is the best choice, whereas at regional and national levels, one may use 1000, 100,000 or million as multiplier. For common, minor vaccine reactions, percentage is recommended and for rare serious reactions, 10,000, 100,000 or 1,000,000 (million) can be used.

8.5 Interpretation of data

Available expected rates for each type of AEFI for a given antigen is provided at https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health

professionals-info/reaction-rates-information-sheetsThis can help to make decision on corrective action to be taken on reported AEFIs. It is also important to know about background rates of reported medical events in the country. Comparison of background rates with reported rates of AEFI will guide to a possible hypothesis of a coincidental event. For example, febrile seizures with bacterial or viral infection etiologies are common among young children and may also occur following some vaccines such as DTwP. Therefore, it is important to know the rate of febrile seizures due to other reasons and expected rates following a given antigen.

If the values exceed the expected background rates, then one should consider true increase or coincidence due to ongoing other diseases.

8.6 Evaluating the performance of the AEFI surveillance system

The immunization safety surveillance system should be continuously monitored and also regularly evaluated. The purpose is to identify gaps and rectify them in order to strengthen the immunization safety surveillance system in the country. The evaluation should be based on performance, quality and responses.

1. To monitor the **performance** of the AEFI surveillance system the following indicators will be used:
   a) AEFI reporting rate per 100 000 population
   b) AEFI reporting rate per 100 000 < 5 population
   c) AEFI reporting rate per 1 000 000 distributed doses of vaccines
   d) AEFI reporting rate per 1 000 000 administered doses of vaccines
   e) percentage of serious AEFI cases versus total AEFI reports;
2. To monitor the **quality** of AEFI reporting:
   a) completeness of reports (% of AEFI report forms with completed critical information)
   b) timeliness of reports (% of serious AEFI reports received as per specified time);
3. To monitor the **response** to serious AEFI:
   a) Timeliness of case investigation (% of serious AEFI cases investigated within 48 hours of occurrence).

The Standard indicator for Tanzania is 10 AEFI cases per 100, 000 surviving infants per year.

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 to determine the quality of death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or life-threatening districts and regions are encouraged to achieve a target of at least 1 serious case per 10,000 live births per year.

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

a) Timeliness and completeness of AEFI reporting
b) Percentage of AEFI cases reported on time (< 24 hours of notification) to the national level
c) Number (%) of AEFI investigation conclusions supported by findings of special tests (clinical specimens, Post- mortem findings (among AEFI deaths), lab findings for vaccine samples).
d) Number (%) AEFI cases where final classification including causality assessment by AEFI committee is completed within 30 days of receipt of all documentation from districts.
e) Number (%) AEFI cases reviewed by National AEFI committee following receipt of reported AEFI cases from region at National level.

f)Number (%) AEFI cases reviewed by National AEFI committee and not assessable due to lack of information.

g) Response to AEFI by the program particularly those related to programme error.

h) Percentage of investigated AEFI with feedback from national (TMDA and IVD) to RHMT and CHMT within seven (7) days of conclusion of investigation

g) Percentage of investigated AEFI with feedback from RHMT/CHMT to the community within fourteen (14) days of conclusion of investigation

9.0 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 programme.

Causality assessment is important for:

a) Identification of vaccine-related problems;
b) Identification of immunization error-related problems;
c) Excluding coincidental events;
d) Detection of signals for potential follow-up, testing of hypothesis and research; and
e) Validation of pre-licensure safety data with comparison of post-marketing surveillance safety data.

9.1 Criteria for Case selection for causality assessment

Not all AEFI incidents that are reported need to be subject to a formal causality assessment. In some cases, it becomes immediately clear that symptoms began before the vaccination. The causality assessment should be done for the following:

a) Severe and Serious AEFI
b) Clusters and events above expected rate/ severity
c) Evaluation of suspected signals
d) Other AEFI (if required) as decided by reviewing team / committee including:
i) If immunization error is suspected (e.g. bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome);
ii) Significant events of unexplained cause within 30 days of vaccination (and not listed in the product label)
iii) Events causing significant parental or community concern (e.g. HHE, febrile seizures).

9.2 Preparation for causality assessment

Prior to causality assessment,

a) The AEFI case investigation should have been completed
b) All details of the case such as case report form, case investigation form, completed clinical case record, lab reports, autopsy report, details of field investigations etc. should be available at the time of assessment
c) There must be a “valid diagnosis” which is the extent to which the unfavorable or unintended sign, abnormal laboratory finding, symptom or disease is defined.

With inadequate or incomplete case information, an adequate causality assessment cannot be performed or if attempted, the AEFI may be deemed unclassifiable or not assessable due to lack of information. On the other hand, even with complete information the AEFI may be categorized indeterminate due to the lack of clear evidence of a causal link, or conflicting external evidence or other inconsistencies. Nevertheless, these assessments 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.

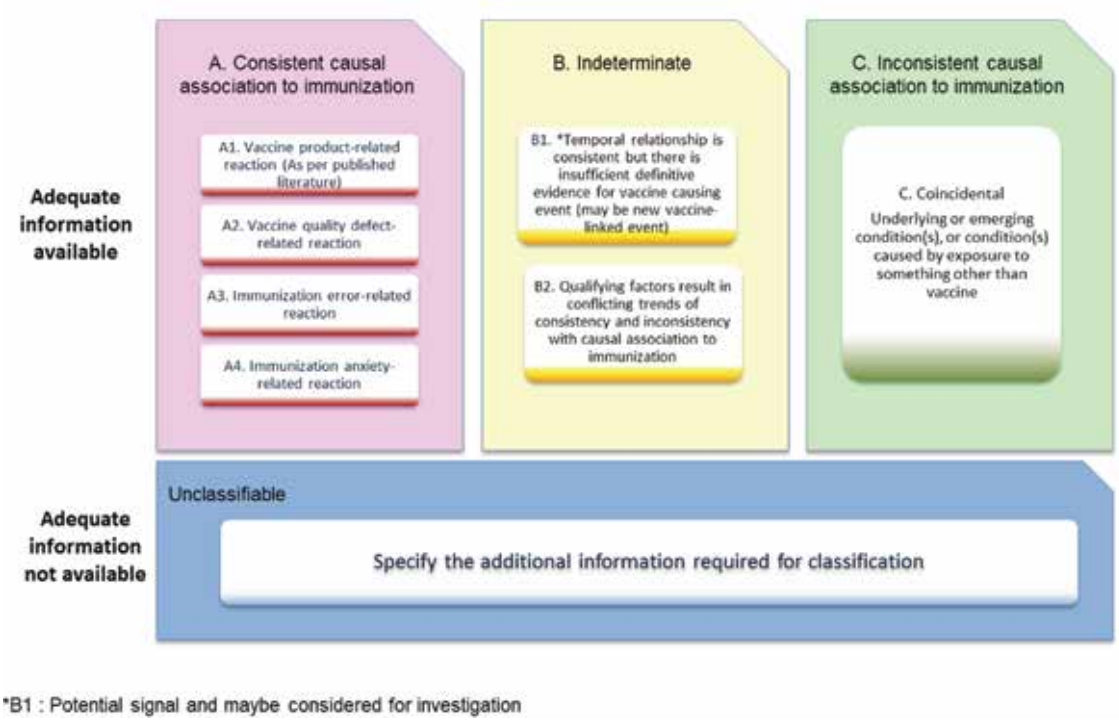


Figure 7: Final classification of cases after determining causality

9.3 Causality assessment team

Causality assessment in Tanzania is done by a reviewing team/ committee at the national level that is

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

The committee has a written Terms of Reference (ToR). In summary, causality assessment of serious cases needs high levels of expertise and will be done by an expert committee only at the national level. 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.

A comprehensive guide and background to causality assessment has been published by WHO and can be accessed online at http://www.who.int/vaccine_safety/publications/gvs_aefi/en/.

10.0 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/expert committees.

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 using standard AEFI reporting form. In case patients need hospitalization, existing referral system should be used.

Depending on the nature of the event(s), the number of people affected, and community perceptions, an investigation may be conducted. In general, it is not advisable to discontinue the immunization programme while awaiting the completion of the investigation. If AEFI causality is not established – depending on the nature of the event, its extent and whether it is ongoing – a further investigation or epidemiological study may be warranted (Table 16). However, it must be accepted that in some cases the relationship to vaccine will never be clear.

Table 16: 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, TMDA will obtain information from the manufacturer and may consult with the WHO regional office 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: Improve 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

Type of AEFI	Follow-up action
	the event was caused by immunization. Sometimes, it may be useful to enlist further expert investigation to ensure that the event was truly coincidental. The potential for coincidental events to harm the immunization programme through false attribution is immense.

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

10.1 Management of suspected anaphylaxis or collapse after vaccination

Sudden and severe events occurring post-vaccination, especially syncope, are frequently reported as anaphylaxis. However, anaphylaxis following vaccination is very rare and the risk (in general) is 1−2 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 center 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 17** lists conditions which may be mistaken for anaphylaxis.

Table 17: 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 2−6 hours 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 viral 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.

11.0 COMMUNICATION AND MEDIA MANAGEMENT

11.1 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.

11.2 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 8)** illustrates some of factors that may trigger public concerns; hence the need for improved quantity, quality and targeted communication about vaccine safety.

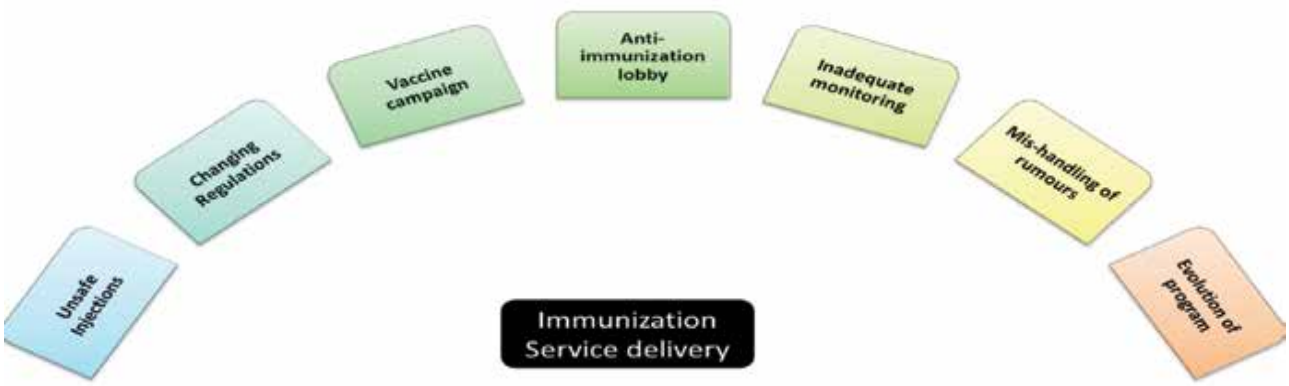


Figure 8: Factors triggering public concerns to immunization

Challenges to effective communication

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

a) Decline of childhood infections and deaths from vaccine preventable diseases (VPD)
b) Parents view that infectious disease is a thing of the past
c) Introduction of new vaccines and related information gaps
d) Mass campaigns or Supplemental Immunization Activities (SIAs)
e) Need for transparency and accountability

11.3 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;

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

11.4 Role of Health Care Worker in Community Communication on AEFI

AEFI can have repercussions on the entire routine immunization programme 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 Programme in the long-term. Messages relating to adverse events must be disseminated rapidly to prevent rumours from spreading.

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

a) Communicate immediately with the DIVO/District Pharmacovigilance Personnel
b) 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.
c) 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.
d) If the AEFI was caused by immunization error, tell the public what steps are being taken to prevent similar events in the future.
e) Constantly reassure the public of the safety of vaccines.

11.5 Communicating with health care worker

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

11.6 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 national immunization programme. Depending on the need stakeholders mentioned, the following stakeholders will be given preliminary information at initial stage and final report after completion of investigation and causality assessment at a later stage: ICC (Inter-agency Coordinating Committee), Tanzania Medicines and Medical Devices Authority (TMDA), RHMT and CHMT, AEFI Committees at all levels, Politicians, Professional associations, Universities and hospitals, International agencies and development partners and manufacturers.

11.7 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 mass campaign. In the long-term, building partnerships with the media is key to keep the public regularly informed about immunization, its benefit and to motivate families and communities to make use of immunization services.

11.8 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 programme.

11.9 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.

11.10 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.).

11.11 Draft media release

The draft media release must specifically answer the 6 W's for journalists:

a) Who is affected/is responsible?
b) What has happened?
c) What is being done?
d) Where has it happened?
e) When did it happen?
f) Why did it happen?

g) 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).

11.12 A spokesperson system

The district level shall be the first authority in releasing the information to the media. For this purpose, the District Medical Officer shall be responsible for communicating the AEFI to the media, public and stakeholders at district level. This limits the possibility of conflicting messages coming from different sources. Ensure spokesperson has the important information.

If the AEFIs involved two or more districts within a region, the Regional Medical Officer will be responsible for communicating to the media, public and the stakeholders in that region. Similarly, if the cases warrant communication to the whole nation, then the higher authorities will be responsible.

a) Analyze rumor, its level and potential to cause damage.
b) Anticipate how situations might evolve following response; prepare before responding.
c) 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.
d) 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.
e) Plan how to prevent future rumors.
f) Prepare a media release

An effective media release should include a complete account of the event, framed in its context (e.g. an isolated event or a cluster of AEFI or coincidental event). The media release should have;

a) An outline of actions taken or planned (such as the AEFI investigation).
b) A description of the cause of the event (but only when this is known with certainty).
c) An assurance that corrective action has been taken or will be taken.
d) Reference to any relevant publication, video material or web site.
e) Sender's name and spokesperson's details.
f) Limited to one page of matter (400-500 words max).
g) 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.

11.13 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:

a) AEFI Committee takes the lead but identifies who facilitates the press conference.

b) If there are several members on the panel, agree beforehand on the key message(s) in response to the AEFI.

c) Agree on roles of each panel member beforehand, including the type of questions (media, political etc.) each panel member may best handle.

d) Panel members must avoid contradicting each other in the press conference unless it is critical to clarify something incorrect that has been said.

e) 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.

11.14 Media Management post AEFI

11.14.1.1 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.

11.14.1.2 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.

11.14.1.3 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 though a press release or hard copy document. The website of the Ministry of Health can also be used to update the media.

11.15 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 programme. Once rumours start they can be very hard to stop.

Some examples of rumours include: “vaccines are a contraceptive to control population”, “vaccines are contaminated by the HIV or a mad cow disease” and “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 travel quickly beyond your local area.

11.15.1.1 Common causes of rumours

Common causes of rumors include but not limited to the following:

a) Inadequate information sharing by health care providers,
b) Failure to communicate correct information about vaccine effects and schedules,
c) Failure to check whether caregivers know and understand information,
d) Failure to give clients opportunities to ask questions and
e) Parents/caregivers' negative attitudes about immunization services.

11.15.1.2 What you can do at the health facility

Under the direction of your supervisor:

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

11.15.1.3 Words of advice

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

Bibliography

1. Tanzania Medicines and Medical Devices Act, Cap 219
2. Tanzania Medicines and Medical Devices (Pharmacovigilance) Regulations, 2018
3. https://www.who.int/vaccine_safety/committee/reports/June_2018/en/
4. WHO, Global manual on surveillance of adverse events following immunization, March 2016

12.0 ANNEXES

Annex 1. AEFI reporting form

TMDA/DMC/CTP/F/010

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

AEFI REPORTING FORM

(Made under regulations 33, 36(1)(a), 38(1), and 46(1)

***Patient name*:** ***Patient's full Address*:** Telephone : Sex: M F (Pregnant ☐ Lactating) ***Date of birth (DD/MM/YYYY)*: _ _/_ _/_ _ _ _** *OR Age at onset : Years Months Days* *OR Age Group:* 0 < 1 year > 5 years - 18 years 1- 5 years > 18 years – 60 years > 60 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 of vaccine (Generic)	***Brand Name incl. Name of Manufacturer***	***Date of vaccination***	***Time of vaccination***	Dose (1st, 2nd, 3d etc.)	***Batch/ Lot number***	Expiry date	***Batch/ Lot number***	Expiry date	Time of reconstitution

Adverse event (s):	**Describe AEFI (Signs and symptoms):**
☐Severe local reaction ☐*>3 days* ☐*beyond nearest joint* ☐Seizures ☐*febrile* ☐*afebrile* ☐Abscess, ☐Sepsis ☐Encephalopathy, ☐Toxic shock syndrome, ☐ Thrombocytopenia ☐Anaphylaxis ☐Fever≥38°C	

☐Other (specify)..... Date & Time AEFI started (DD/MM/YYYY): _____/_____/_____ _____Hr___Min	

***Serious: Yes / No;** If Yes ☐Death ☐Life-threatening ☐Disability ☐Hospitalization ☐Congenital anomaly ☐another important medical event (Specify_____)

***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 the history of similar reaction or other allergies), concomitant medication and dates of administration (exclude those used to treat reaction) other relevant information (e.g. other cases). *Use additional sheet if needed:*

TMDA Zonal or Pharmacovigilance Centre to complete

Investigation needed: ☐ Yes ☐ No	If yes, date investigation planned (DD/MM/YYYY): __ __ / __ __ / __ __ __ __

TMDA National Level to complete

Date report received at the national level (DD/MM/YYYY): __ __ / __ __ / __ __ __ __	AEFI worldwide number (VIGIFLOW) ID:

How to report?

- Dully fill in the form as required
- Use a separate form for each patient
- Report direct to AUTHORITY through the following addresses:-

Mail :
Tanzania Medicines and Medical Devices Authority,
P. O. Box 77150, Dar es Salaam
Fax:: 22- 2450793
Phone: 22-2450512 / 2450751/ 0658 445222

Internet;
http://www.tmda.go.tz
E-mail: adr@tmda.go.tz

The AEFI reporting form and the guidelines are also available for

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TO:
THE DIRECTOR-GENERAL
TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY
P. O. BOX 77150 DAR ES SALAAM

downloading at
http://www.tmda.go.tz

Annex 2: AEFI Investigation form

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

AEFI INVESTIGATION FORM FOR COVID -19 AND ROUTINE IMMUNIZATION

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

SHOULD BE FILLED WITHIN 7 DAYS UPON NOTIFICATION

Section A	**Basic details**		
Region	**District**	**Case ID**	**Vigiflow ID**
Place of vaccination *(□)*: Govt. health facility ☐ health facility ☐ Other (specify) ☐ _____		Private	
Vaccination in *(□)*: Campaign			Routine
Name and address of the vaccination facility:			
Name of Reporting Healthcare Worker:		Date of investigation: ___/_____/_____	
Designation / Position :		This report is *(□)*: *First* *Interim* *Final*	
Telephone # landline (with code):		Mobile: e-mail:	
Patient Name			Sex □ M □ F

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

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

OR *Age at onset:__years____months_____days*

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

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

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

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

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

Status on the date of investigation

(□): Died □Disabled □Recovering □Recovered □completely

□Unknown

If died, date and time of death *(DD/MM/YYYY)*:_____/_____/__ (*hh/mm*
Autopsy done? (□) Yes (date)_____ No Planned on (date)_____Time_____

Section B	**Relevant patient information prior to immunization**	
Criteria	**Finding**	**Remarks (If yes provide details)**
Past history of similar event?	Yes / No / Unkn	
Adverse event after any previous vaccination(s)?	Yes / No / Unkn	
History of allergy to vaccine, drug or food?	Yes / No / Unkn	
Pre-existing comorbidity/ congenital disorder?	Yes / No / Unkn	
Pre-existing acute illness (30 days) prior to vaccination?	Yes / No / Unkn	
Has the patient tested Covid19 positive prior to vaccination?	Yes / No / Unkn	

History of hospitalization in last 30 days, with cause?	Yes / No / Unkn	
Was the patient receiving any concomitant medication? (If yes, name the drug, indication, doses & treatment dates)	Yes / No / Unkn	
Family history of any disease (relevant to AEFI) or allergy?	Yes / No / Unkn	
For adult women Currently pregnant? Yes (weeks)_____/ No / Unknown Currently breastfeeding? Yes / No		

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

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

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

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

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

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

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

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

If patient has received medical care □ attach copies of all available documents (including case sheet, discharge summary, laboratory reports and autopsy reports, if available) and write only the information that is not available in theattached documents below

If patient has not received medical care – obtain history, examine the patient and write down your findings below (addadditional sheets if necessary)

Provisional / Final diagnosis:

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

	□			□						
□ Number immunized for each antigen at session site. Attach record if available.	/accine name			□				□		□
	Numberof doses									

a) When was the patient immunized? (□ the below and respond to ALL questions)	
Within the first vaccinations of the session Within the last vaccinations of the session Unknown	
In case of multidose vials, was the vaccine given within the first few doses of the vial administered? within thelast doses of the vial administered? unknown?	
Was there an error in prescribing or non-adherence to recommendations for use of thisvaccine?	Yes□ / No
Based on your investigation, do you feel that the vaccine (ingredients) administered could havebeen unsterile?	/ 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?	/ 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, impropermixing, improper syringe filling etc.)?	/ 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.)?	/ 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.)?	/ No / Unable to assess
h) Number immunized from the concerned vaccine vial/ampoule	
i) Number immunized with the concerned vaccine in the same session	
Number immunized with the concerned vaccine having the same batch number in otherlocations. Specify locations:	
k) Could the vaccine given to this patient have a quality defect or is substandard or falsified?	/ No / Unable to assess
Could this event be a stress response related to immunization (e.g. acute stress response,vasovagal reaction, hyperventilation, dissociative neurological symptom reaction etc.)?	/ No / Unable to assess
m) Is this case a part of a cluster?	Yes□ / No / Unkn
i. If yes, how many other cases have been detected in the cluster?	
a.Did all the cases in the cluster receive vaccine from the same vial?	Yes□ / No / Unkn
b.If no, number of vials used in the cluster (enter details separately)	

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

Section E Immunization practices <u>at the place(s) where concerned vaccine was used</u> ***(Complete this section by asking and/or observing practice)***	
Syringes and needles used:	
Are AD syringes used for immunization?	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)			
Reconstitution procedure (□)	Status		
Same reconstitution syringe used for multiple vials of the 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 using the same as those recommended by the manufacturer?	Yes	No	NA
Specific key findings/additional observations and comments:			
Injection technique in vaccinator(s): (Observe another session in the same locality – same or different place)			
Correct dose and route?	Yes / No		
Time of reconstitution mentioned on the vial? (in case of freeze-dried vaccines)	Yes / No		
Non-touch technique followed?	Yes / No		

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

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

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

Section H Other findings/observations/comments

Annex 3: AEFI line list

S. No	Patient Name/ Identifier	Health facility	District	Sex (M/F)	Age (Date of brith or age at onset)	Vaccine/s	Vaccine Batch No	Diluent Batch No	Adverse Event	Date of Vaccination (DOV)	Date of onset (DOO)	Date of Reporting (DOR)	Serious (Yes/ No)	Reason for Serious	Autopsy (Y/N/ NA)	Reporter and Contact	Investigation Planned (Y/N)	Date report recd. at Natl Level	Causality Assessment*
1																			
2																			
3																			
4																			
5																			
6																			
7																			
8																			
9																			
10																			
11																			
12																			
13																			

S. No	Patient Name/ Identifier	Health facility	District	Sex (M/F)	Age (Date of birth or age at onset)	Vaccine/s	Vaccine Batch No	Diluent Batch No	Adverse Event	Date of Vaccination (DOV)	Date of onset (DOO)	Date of Reporting (DOR)	Serious (Yes/ No)	Reason for Serious	Autopsy (Y/N/ NA)	Reporter and Contact	Investigation Planned (Y/N)	Date report recd. at Natl Level	Causality Assessment*
14																			
15																			
16																			
17																			
18																			
19																			
20																			
21																			
22																			
23																			

S. No	Patient Name/ Identifier	Health facility	District	Sex (M/F)	Age (Date of birth or age at onset)	Vaccine/s	Vaccine Batch No	Diluent Batch No	Adverse Event	Date of Vaccination (DOV)	Date of onset (DOO)	Date of Reporting (DOR)	Serious (Yes/ No)	Reason for Serious	Autopsy (Y/N/ NA)	Reporter and Contact	Investigation Planned (Y/N)	Date report recd. at Natl Level	Causality Assessment*
24																			
25																			

Annex 4: Quick guide on AEFI Investigation

QUICK GUIDE ON AEFI INVESTIGATION

Adverse Event Following Immunization **(AEFI)** Is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The AEFI may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

Surveillance of AEFI is important in protecting public health and helps to maintain and improve public confidence in national immunization programmes. Surveillance of AEFI is a cycle which includes **a system for AEFI detection**; **AEFI notification (reporting); AEFI investigation**; **analysis of AEFI data**; **causality assessment** and **providing relevant feedback as well as taking corrective actions.**

Purpose: This aide-mémoire proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI by:
confirming a diagnosis and timing
identifying details of vaccine(s) administered
documenting the outcome of the reported adverse event
determining whether the reported event is solitary or part of a cluster
reviewing the operational aspects of the programme

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

There are 5 possible causes of AEFI:

1. **Vaccine product-related reaction:** an event that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
2. **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.
3. **Immunization error-related reaction:** An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable
4. **Immunization anxiety-related reaction:** an AEFI arising from anxiety about the immunization

WHO SHOULD INVESTIGATE AEFI?

In most cases, a preliminary **investigation** of an AEFI can be made by the health workers at the facility level with support from the district level.

An investigation team should at least be composed of a medical doctor, a staff from reproductive and child health, a pharmacist or a drug store keeper. For some cases investigation should be done by next/higher administrative level, by a trained/skilled person/ team, depending on the nature of event, its seriousness and impact to the program

WHEN TO INVESTIGATE AEFI?

If a detailed investigation is warranted, it should be initiated as soon as possible, ideally within 24 to 48 hours of the case being first reported to the health system.

☑ CHECKLIST FOR AEFI INVESTIGATION

Be prepared
Read the resource documents on AEFI reporting, management and investigation of AEFIs.
Familiarize with the standards: case definitions for reportable AEFIs, use of reporting forms and investigation procedures.
Designate and train staff to conduct an AEFI investigation
Train staff on how to collect specimens.
Notify the higher level (district, region or national) on all steps of investigation
Once initiated, the District/Regional investigator should inform the IVD and TMDA on the status and progress of the investigation
When needed, the national level (Ministry of Health) should deal with communication to the public.
The designated person by the ministry should be the spokesperson of the government to the media and the public about the investigation.

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

Investigate and collect data
Obtain information from patient or relatives dire
available records
Obtain information from immunization service prov
medical care service providers (hospital staff)/ use

3.1 Key Data to be Collected

☑ **Data on each patient**

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

☑ **Data about the vaccine(s) (and diluent if applicable) administered to the patient**

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

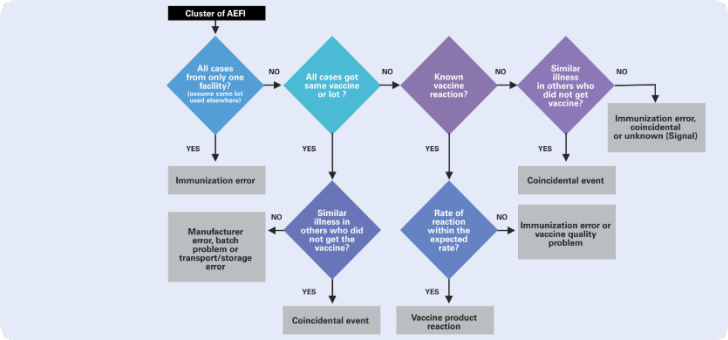
☑ **Programme-related data**.

Common practices in storing and handling vaccines, and vaccine administration in the health centre in which the suspected immunization (or immunizations) were given. This may help identify products mistakenly

INVESTIGATING DEATHS AFTER IMMUNIZATION

After informing higher authorities, field investigation should be conducted by a team of clinical, laboratory and forensic experts supported by DIVO/RIVOs. A decision on autopsy should be taken within the local sociocultural, religious, and political context. Autopsies should be done with adequate information of the circumstances of the event using standard autopsy protocols. Appropriate specimens should be collected for testing.
If an autopsy is not possible, a verbal autopsy can be carried out using established guidelines and protocols.

INVESTIGATION OF CLUSTERS



OUTCOME OF AEFI INVESTIGATION

On concluding the investigation, the documents and evidence collected should be compiled, a report prepared and submitted to a group of experts to determine/evaluate causality.

Important

Overarching goal of an investigation is to identify the system problems and not to blame the individuals
The investigation should start immediately within 48 hours of notification, this is in order to determine the cause, identify additional cases and prevent the occurrence of more cases through institution of effective intervention measure.
Investigation should be conducted systematically through reviewing essential medical records and collect all necessary information and filling the

used instead of vaccine or diluent ☑ **Background data** Establish if cases have been reported from elsewhere and actively look for additional cases among other vaccinees and at large in the community **ANALYSE THE DATA** Review epidemiological, clinical, and laboratory findings Share findings with national AEFI committee for expert advice Summarize and report findings **TAKE ACTION** The response after an AEFI investigation should be based on findings (data/information). The highest priority is to treat patient. Suspending vaccination at the locality of the event temporarily pending investigation outcome may be necessary but is uncommon. Broader suspension of vaccination is only very rarely necessary When taking action, it is important to consider the following Provide feedback to health staff Communicate findings and action to the parents and public – during all stages of the investigation Correct problem (based on the cause) by improving train- ing, supervision and/or distribution of vaccines/injection equipment Replace vaccines if indicated	AEFI investigation form. Investigation should adhere to the principals of epidemiology. Unless it is clearly indicated by the epidemiologic investigation, collecting of vaccine sample for laboratory testing should not be conducted routinely. When collected a cold chain system should be maintained throughout. Investigator team should have access medical records including past medical history of the patient prior to AEFI occurrence Alternative etiologies should be first ruled out before suspecting the vaccine (product related reaction) The fact that an adverse event of the same nature has been previously related to a particular vaccine does not always mean that the case under investigation is also related to the vaccine Have direct discussions with the patients or parents if possible Once initiated, the District/Regional investigator should inform the IVD and TMDA on the status and progress of the investigation Investigation report including AEFI investigation forms including all essential medical records should be sent to TMDA within seven (7) of investigation The role of investigation is to collect evidence to assist in causality assessment. Causality assessment of AEFI is conducted by the Vigilance Technical Committee. Additional information on the definitions, monitoring, management and investigation of AEFIs can be obtained from the IVD/TMDA Offices

Annex 5: AEFI Laboratory Requisition Form

AEFI L A B O R A T O R Y REQUSITION FORM (lLRF) (To be completed by AEFI Investigation team. LRF should be accompanied with specimens)
(For Serious Adverse Events Following Immunization)
AEFI category (Encircle): Death / Hospitalized / Cluster/ Disability

Region										Case ID .																					
Council																															
Village/Street																															
Name of the 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 month)																			Sex	Male	Female
Complete Address of the patient with landmarks (Street name, house number, village, block, Telephone No. etc.)																															
PHONE																															

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)

Mention vaccine/ diluent	Quantity Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufa cturing Date	Expir y Date

b) For vaccine supplies: (AD, Reconstitution, Disposable syringes)

Mention vaccine supplies	Quanti- ty Sent	Name of Manufacturer (in BLOCK Letters)	Batch No.	Manufa-cturing Date	Expiry Date

c) For Biological product specimen: (CSF, Blood, Urine, etc)

Type of specimen:
2. Test requested:
3. Preliminary clinical diagnosis (working hypotheses):

4. Name & complete address of officials to whom laboratory results should be sent:

Send to	Complete address	Phone/ Fax	Mobile	Email -ID
National Level				
Regional				
Council level				
Others (specify)				
To be completed by lab officials after receiving the specimen				

Date of receipt of specimen at laboratory	*D*	*D*	*M*	*M*	*Y*	*Y*	*Y*	*Y*

Name of person receiving specimen(s) at laboratory	

Condition of specimen upon receipt at lab (*encircle*)	Good	Poor	Unknown

Comments by pathologist, virologist or bacteriologist:

Date specimen results sent from this lab	D	D	M	M	Y	Y	Y	Y

Name of laboratory	

Signature

Phone number:

Email Address:

12.1.1.1 Establishing codes for area, reaction type, cause of AEFI, and certainty of cause will facilitate recording, data entry and analysis. Because of the potential for coding errors, the code should be double-checked.

Coding for cause of AE FI:

[A1] Vaccin e- related	[A2] Immuniz ation error-	[A3] Immuniza ti on anxiety-	[B] Indeter min- ate	[C] Coinciden t- al	[D] In adequa- Te Information